SCIENCE

AUGUST 8, 1952

VOLUME 116 NUMBER 3006

Contents

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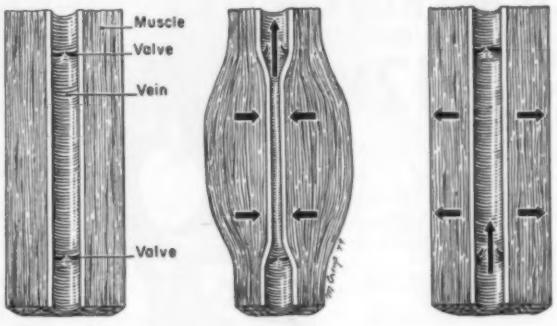

Fig. 77. The action of skeletal muscles in moving blood through the veins. *A*, Resting condition. *B*, Muscles contract and bulge, compressing veins and forcing blood toward heart. The lower valve prevents backflow. *C*, Muscles relax, and the vein expands and fills with blood from below; the upper valve prevents backflow.

Simple?

It would be pretty difficult to present the concept of blood flow any more simply or clearly than it is presented above.

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Dr. Claude Villee's book—**Biology: The Human Approach**—is written on that assumption. It is clear and interesting, as thousands of students will attest, but it also presents all the information that should be acquired in the college course. The author says, on this score: "Most students find the facts of life so interesting that a superficial treatment is both unnecessary and an affront to their intelligence."

If you haven't used the VILLE book, Professor, why not get it down from the shelf and take a good look at it? Or, if you haven't seen it, write for an examination copy?

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SCIENCE

Human Hemoglobin

INVESTIGATIONS in our laboratories on human hemoglobin during the past four years have shown that the erythrocytes of an individual may contain two, and even three, different molecular species of hemoglobin. Ten genetically distinct conditions that may be characterized by the hemoglobin composition of the erythrocytes have been observed. Some of these conditions are associated with severe anemias, but others are difficult, if not impossible, to detect on the basis of clinical observations. It is therefore of importance in physical and chemical studies on human hemoglobin that the investigator utilize individual rather than pooled specimens.

It has been known for many years that the fetus of a given species produces a hemoglobin which differs from that produced by an adult member of the same species. The discovery of an electrophoretically abnormal hemoglobin in sickle cell disease in 1949 (Pauling, Itano, Singer, and Wells) provided the first positive evidence that adult hemoglobin may exist in more than one molecluar form. The following year a second abnormal adult hemoglobin was discovered, again by the use of electrophoretic mobility measurements. A third abnormal adult hemoglobin was detected last year by the combined use of electrophoretic mobility and solubility measurements. No abnormal fetal hemoglobin is known to exist, but recent investigations in this country and in Europe have shown that in certain anemic states the diseased individual may produce normal fetal hemoglobin beyond the age at which it is present in healthy individuals.

The available evidence indicates that an individual inherits a genetically controlled mechanism for the synthesis of hemoglobin from each of his parents. The great majority of individuals have inherited a normal mechanism from each parent, and their erythrocytes contain only normal adult hemoglobin except in the first few months of postnatal life, when fetal hemoglobin is also present. Whenever an abnormal adult hemoglobin is present in an individual, investigation of his parents has demonstrated the presence of the same abnormal form in one or both of them. Matings of two individuals who possess different abnormal adult hemoglobin may result in children who have either or both the abnormal forms. On the other hand, many individuals with chronic, inherited anemias have fetal hemoglobin in addition to one or two of the adult hemoglobins, but their parents have no fetal hemoglobin. The hypothesis has been advanced that the production of fetal hemoglobin beyond early postnatal life may represent a compensatory response to the anemic state.

Among individuals who have the sickle cell trait—i.e., those whose erythrocytes contain both normal adult and sickle cell hemoglobins—a wide variation in the ratio of concentrations of the two forms has been observed. The results of familial studies of this ratio are consistent with a hypothesis that different normal alleles may exist in the human population which control the production of normal hemoglobin at distinctive rates.

Simple, rapid tests for the detection of the different normal and abnormal hemoglobins and their mixtures are needed, both for chemical and genetic studies. Fetal hemoglobin is most readily differentiated from all the adult hemoglobins by its high resistance to denaturation in aqueous alkaline solutions. The presence of sickle cell hemoglobin is indicated by the sickling of erythrocytes upon deoxygenation. Recent investigations here have demonstrated the usefulness of solubility determinations in the detection of the second abnormal hemoglobin.

The study of abnormal hemoglobins undoubtedly will continue to be a fruitful field for collaboration among chemists, geneticists, and hematologists. It has not been feasible in this brief report of recent work in these laboratories to acknowledge the contributions of the many laboratories elsewhere that are engaged in human hemoglobin studies.

HARVEY A. ITANO
Gates and Crellin Laboratories of Chemistry
California Institute of Technology

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7. Exhibitors in the 1952 Annual Exposition of Science and Industry and descriptions of their exhibits.

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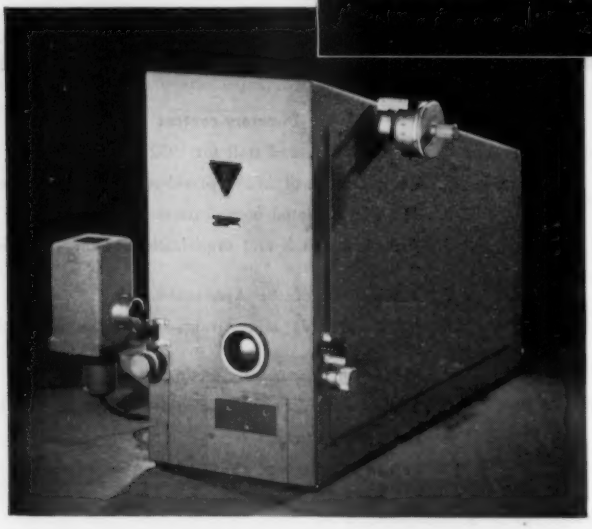

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The Chemical Approach to the Control of Tuberculosis[1]

H. Herbert Fox
Hoffmann-La Roche Inc., Nutley, New Jersey

ALTHOUGH THE VIVIDLY DESCRIPTIVE NAME "white plague" has long since gone out of fashion in designating tuberculosis, it is worth remembering that the disease itself is still very much with us. In disclosing his discovery of the tubercle bacillus in 1882, Koch (*1*) pointed out that tuberculosis was the greatest killer of human beings among all the diseases. What Koch said then is still true today, despite the tremendous strides made in the chemotherapy of bacterial infections. It is estimated that 5–6 million people are killed yearly throughout the world by the tubercle bacillus.

The tuberculosis problem. Under the impetus of such a tremendous spur, it might seem strange that so little has been accomplished in controlling the disease, but the uncomfortable fact is that the fungus-like organism has proved to be practically immune to the many chemotherapeutic agents that are so spectacularly effective against other bacteria. The common antibiotics such as penicillin, aureomycin, terramycin, and chloramphenicol, as well as the host of active "sulfa" drugs, are without significant effect in tuberculosis. In this intractableness, tuberculosis is almost unique among bacterial diseases. It is difficult to overemphasize this point, because the whole problem of its chemotherapy has hinged upon this outstanding and deplorable characteristic. It has also been responsible, in part, for a major misconception concerning the structure of the tubercle bacillus which has plagued workers engaged in the search for antitubercular agents. According to the generally accepted concept, the intractable character of the tuberculous infection and the resistance of the tubercle bacillus to chemotherapeutic agents were due to a waxy capsule surrounding the organism (*2, 3*). On the assumption that penetration of the organism by the drug was an essential prerequisite for antitubercular activity, it seemed reasonably certain that the desired therapeutic effect could be achieved only with fat-soluble materials, which could penetrate through the waxy envelope. We know now that fat-solubility is not required. Indeed, all the effective tuberculostats known to date are either water-soluble or are highly polar molecules of the type associated with water-solubility rather than fat-solubility. Nonetheless, some experimentalists still stress the positive influence of a high lipid/water distribution ratio on the inhibitory action of their compounds.

Another difficulty inherent in the tuberculosis problem is the fact that the host-parasite relationship is different from that found in the common bacterial infections. In the latter type, the struggle between the host and the parasite is an acute, all-or-none affair, with one or the other quickly succumbing. Since the advent of modern chemotherapy, the struggle has been shortened still further, and the issue is generally decided in favor of the host. On the other hand, most tuberculosis is chronic in character, and the tubercle bacillus can remain viable in the host for long periods without provoking a fulminating, all-or-none struggle. Moreover, the host's defensive mechanisms seem slower and less certain, so that even though the disease process has been slowed or suppressed by means of a tuberculostat the host is not capable of rapidly destroying the invading organism.

The importance of the chronicity of an infection on its susceptibility to treatment was recently stressed by Florey (*4*), who pointed out that staphylococcic osteomyelitis, upon early diagnosis and treatment, before tissue destruction has occurred, can be controlled by penicillin alone. In the later stages, when an abscess is present, the pus must be drained off before a satisfactory penicillin effect can be obtained. When, still later, the bone becomes chronically infected and dead bone is present, sterilization with penicillin is impossible and surgical removal of the dead tissue is essential. Florey further stated:

> The reason for the failure of penicillin to sterilize slough or dead tissue is not clear, but the fact is worth keeping in mind as we go on to consider the possibilities of chemotherapy of tuberculosis, for penicillin in its own field is a very powerful bactericidal agent compared with agents used against mycobacteria, and the lesions of tuberculosis nearly always contain necrotic tissue.

It would therefore seem that, even though the old concept of a waxy, protective capsule around the tubercle bacillus is untenable, the problem of getting the drug to the organism is still salient because of the mechanical barriers imposed by necrotic and fibrotic tissue, caseation, and incorporation of the bacilli in phagocytes.

As an end result of these difficulties, it is very unlikely that any drug will be found which will cure chronic tuberculosis with the same speed and dispatch

[1] Contribution No. 209 from the Research Laboratories of Hoffmann-La Roche Inc.

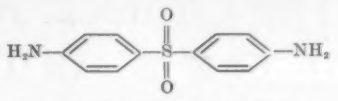
as penicillin, for example, disposes of many acute bacterial infections. Even if the drug were powerfully tuberculocidal, clinical cure would still be relatively slow because of the extensive tissue destruction that accompanies the disease, and because healing and tissue regeneration are in themselves slow processes. Since it is patently obvious that no drug can be expected to restore a destroyed lung, it becomes axiomatic that early diagnosis and treatment are essential corollaries to successful chemotherapy.

The antibiotics. The clinically effective chemotherapeutic agents for tuberculosis may be divided into two principal classes: the antibiotics and the synthetics. Until very recently the most important and most active tuberculostats belonged to the antibiotic class. These were streptomycin, first isolated in 1944 by Schatz, Bugie, and Waksman (*5*), and its hydrogenated derivative dihydrostreptomycin. The latter compound was developed (*6*) in what proved to be an essentially unsuccessful effort to find a less toxic substitute for streptomycin. Both compounds are about equally effective in the treatment of miliary tuberculosis, pulmonary tuberculosis, and tuberculous meningitis and, despite initial expectations, are about equally toxic. The list of toxic reactions attending the use of these drugs has assumed formidable proportions over the years, but perhaps their most serious disadvantage lies in the rapidity with which resistant strains emerge. This phenomenon has militated against their use in minimal cases of tuberculosis on the theory that most such cases would recover with the more conventional regimen, and that it would therefore be unwise to run the risk of developing in them a streptomycin-resistant strain. The necessity of withholding streptomycin or dihydrostreptomycin in the early stages when the disease is most susceptible to chemotherapy is, of course, particularly painful to the clinician, because it is entirely contrary to his concept of what is generally regarded as the ideal practice. More recently, it has been found that the emergence of resistant strains can be delayed by the concomitant administration of *p*-aminosalicylic acid (*7, 8*). An additional disadvantage of streptomycin lies in the fact that some cases, which are apparently suitable for chemotherapy, fail, for some obscure reason, to respond to the drug. These are the so-called intractable cases.

The other antibiotics that have been clinically explored are neomycin (*9*) and viomycin (*10, 11*). Little need be said of these other than that they are less active than streptomycin and hold little promise for the future (*12*).

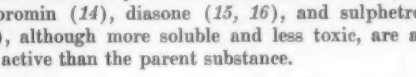
The synthetic tuberculostats. The synthetic tuberculostats may be divided into four principal categories: the sulfones, the aminohydroxybenzoic acids, the thiosemicarbazones, and the pyridine carboxylic acid derivatives.

The sulfones are chronologically the first of the modern synthetic tuberculostats. The tuberculostatic activity of 4,4′-diaminodiphenylsulfone, the parent substance of this group, was first discovered in 1939 (*13*), and since then many attempts have been made to develop sulfones with decreased toxicity and increased solubility and activity. No notable success in

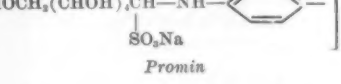


4,4′-Diaminodiphenylsulfone

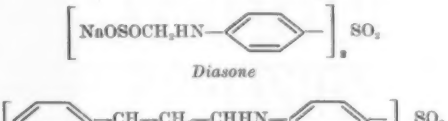
this direction has yet been achieved. Derivatives, such as promin (*14*), diasone (*15, 16*), and sulphetrone (*17*), although more soluble and less toxic, are also less active than the parent substance.



Promin

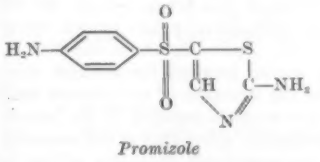


Diasone



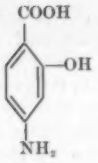
Sulphetrone

It has been suggested, but not proved, that these compounds are active, because they are degraded in the body to 4,4′-diaminodiphenylsulfone. Promizole (*18*), a slightly later development in the sulfone field, appears to be somewhat better than the others (*19*), but clinically all the sulfones leave much to be desired. They are all quite toxic, and none of them is sufficiently tuberculostatic to serve effectively as the sole chemotherapeutic agent in the treatment of clinical tuberculosis. It is interesting to note, however, that promin has been used with some success in Hansen's disease (*20*).



Promizole

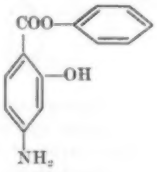
The tuberculostatic activity of *p*-aminosalicylic acid (PAS) was discovered by Lehmann (*21, 22*) in 1944 on the basis of the earlier observations of Bernheim (*23, 24*) that the oxygen uptake of the tubercle bacillus increased under the influence of benzoates and salicylates. The activity of PAS is much lower than that of streptomycin and is limited to pulmonary tuberculosis and tuberculosis of the mucous membranes, but because it is relatively atoxic and can be given safely in large doses, it has found clinical acceptance. Unfortunately, it is rapidly absorbed and



PAS

excreted so that, to maintain adequate blood levels, it must be given in large doses at frequent intervals. Lately, despite its low order of activity and limited usefulness alone, it is being ever more widely used, because, as was pointed out before, there is evidence to show that the appearance of resistant strains is retarded if PAS is given along with streptomycin (*7, 8*).

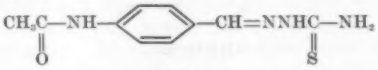
In the normal course of events, many variants of PAS have been prepared and studied, but with one possible exception, none of them has proved to be superior to the parent substance. In 1951, Freire, Rist, and Grumbach (*25*) announced the discovery of FR7 (phenyl *p*-aminosalicylate), a compound that



FR7

was designed with a view to slowing up the overly rapid absorption and elimination characteristic of PAS. According to them, FR7 given orally is no more active than PAS, but on subcutaneous administration in mice in either oil solution or aqueous suspension, it is ten times more active than PAS and is about equal to streptomycin.

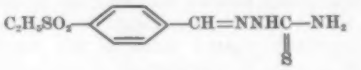
Until very recently the most active of all the synthetic tuberculostats were the thiosemicarbazones. Their discovery by Domagk and his co-workers (*26–29*) constituted a great forward step in the conquest of tuberculosis. Tibione (*p*-acetaminobenzaldehyde thiosemicarbazone), the most prominent mem-



Tibione

ber of this class, is now widely used in Europe, where it has been applied with some success in most forms of tuberculosis. In this country, it has not received much attention, because its use is accompanied by a high incidence of severe side reactions, which include gastric disturbances, anemia, and liver and kidney damage. Another probable reason for its lack of acceptance here is the ready availability of streptomycin, which is generally regarded as a much superior tuberculostat.

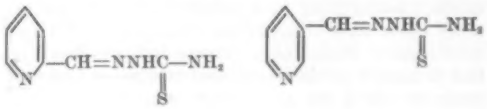
Many variations of the Tibione structure have been made, most of which have involved the character and position of the subordinate grouping on the benzene ring. None of these is superior to Tibione, with the possible exception of the *p*-ethylsulfonyl derivative (Tb III). This compound is not regarded with par-



Tb III

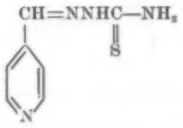
ticular favor by its originators, but some English workers consider it to be more promising than Tibione (*30, 31*).

Replacement of the benzene ring with pyridine results in the pyridine analog of Tibione. The three isomeric forms possible to this structure—picolinaldehyde thiosemicarbazone, nicotinaldehyde thiosemicarbazone, and isonicotinaldehyde thiosemicarbazone —have been prepared and studied, at least preliminarily. The α-isomer (picolinaldehyde thiosemicarba-



α

β



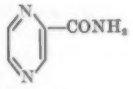
γ

zone) was prepared by the author (*32*) and is too toxic for use. The β-isomer (nicotinaldehyde thiosemicarbazone) was prepared independently in Switzerland (*33*), France (*34*), and the United States (*35*) and, according to the French workers, is much superior to Tibione in animal studies (*34, 36, 37*). These results have been partially confirmed in this country (*38*). The γ-isomer (isonicotinaldehyde thiosemicarbazone) was prepared by the author (*32*) and was found to be comparable in activity to the β-isomer (*38*). In effect, therefore, the β- and γ-pyridylaldehyde thiosemicarbazones were the most potent synthetic tuberculostats known up to that time—particularly if judged by their marked antitubercular efficacy in the intranasal type of infection in mice.

The pyridine carboxylic acid derivatives constitute a relatively new category in the realm of synthetic tuberculostats, and their erstwhile most important member, nicotinamide, has been largely ignored by chemotherapists and tuberculotherapists in this country. The antitubercular activity of nicotinamide equals that of PAS, but it has not gained favor here, perhaps because it is generally anticipated that in the large doses required it would prove too toxic. It is,

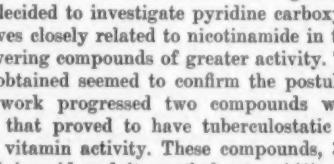
however, being tested more extensively in Europe.

The discovery of the tuberculostatic activity of the vitamin nicotinamide was made by Chorine (*39*) and by Huant (*40*) in 1945. Chorine showed at the time that nicotinic acid, despite its vitamin activity, is not tuberculostatic and thus conclusively proved that there is no relationship between the two types of activities. Oddly enough, this very significant discovery seems to have completely escaped notice in this country. In 1948, the activity of nicotinamide in tuberculosis was rediscovered here by McKenzie and Kushner and their co-workers (*41, 42*) who, in addition, postulated that the activity against the tubercle bacillus is a function of its vitamin activity. This postulate was based on their observation that all the derivatives of nicotinamide that are tuberculostatic also have vitamin activity, whereas those derivatives devoid of one activity are devoid of the other. Perhaps because none of the active derivatives that they prepared were as good as nicotinamide, they appear to have dropped their investigation in this direction. Recently, Kushner *et al.* (*43*) announced the discovery of pyrazinamide (Aldinamide) as a tuberculostat with an activity about three times greater than that of PAS or nicotinamide. Preliminary reports indicate, however, that it quickly produces resistant strains—a fact that seems to rule it out as an effective clinical agent, at least when used alone (*44–48*).



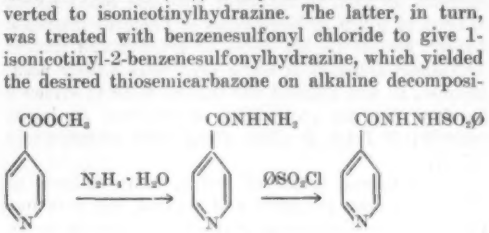
Aldinamide

Intrigued by the postulate of McKenzie, Kushner, *et al.* and unaware of Chorine's work negating it, the author decided to investigate pyridine carboxylic acid derivatives closely related to nicotinamide in the hope of uncovering compounds of greater activity. The first results obtained seemed to confirm the postulate, but as the work progressed two compounds were discovered that proved to have tuberculostatic activity without vitamin activity. These compounds, 3-aminoisonicotinic acid and its methyl ester (*49*), were, to the author's knowledge, the first in the pyridine field,

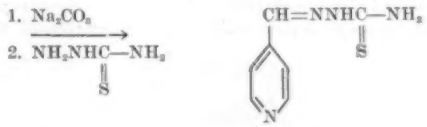


other than nicotinamide and its immediate derivatives, which exhibited *in vivo* antitubercular activity. Although both compounds are only about one half as active as nicotinamide and are of no interest clinically, they served to show that antitubercular activity in the pyridine field is not necessarily limited to derivatives of nicotinamide or to compounds with vitamin activity. This meant, in effect, that the field was wide open and that, theoretically, at least, tuberculostatic activity might exist in any pyridine structure.

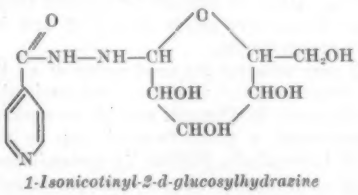
This concept was confirmed subsequently by the marked activity of the β- and γ-pyridylaldehyde thiosemicarbazones. It was in the preparation of the latter compound by the author that the discovery was made of a new class of antitubercular agents of remarkable *in vivo* activity. In preparing isonicotinaldehyde thiosemicarbazone by a modification of the McFadyen-Stevens reaction (*32*), methyl isonicotinate was converted to isonicotinylhydrazine. The latter, in turn, was treated with benzenesulfonyl chloride to give 1-isonicotinyl-2-benzenesulfonylhydrazine, which yielded the desired thiosemicarbazone on alkaline decomposi-



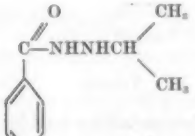
Rimifon



tion in the presence of thiosemicarbazide. Since both the isonicotinic acid hydrazide and its benzenesulfonyl derivative were pyridine carboxylic acid derivatives and therefore closely related to the structures under investigation, they were submitted for testing to the Chemotherapy Laboratories of Hoffmann-La Roche Inc. The benzenesulfonyl derivative was shown to be inactive. On the other hand, the isonicotinic acid hydrazide (Rimifon[2]) proved to have an *in vivo* anti-



1-Isonicotinyl-2-d-glucosylhydrazine



Marsilid

tubercular activity that far exceeded that of any other known substance—whether synthetic or antibiotic. Further investigation of this new type of tuberculostat resulted in the synthesis of 1-isonicotinyl-2-d-glucosylhydrazine and 1-isonicotinyl-2-isopropylhy-

[2] Trade mark of Hoffmann-La Roche Inc.

drazine (Marsilid[2]). Both these compounds were remarkably potent, but the glucosyl derivative proved to be relatively unstable and was withdrawn after brief clinical testing (*50*).

Chemotherapeutic studies by Grunberg and Schnitzer (*51*) indicate that mice infected intravenously with 0.5 ml of a 10^{-3} dilution of a 7–10-day-old culture of *Mycobacterium tuberculosis* in Dubos medium are protected in 50 per cent of the cases (PD_{50}) by a daily dose of 4.6 mg/kg Rimifon in the diet, whereas the PD_{50} is 6.2 mg/kg in mice infected intranasally with 4 drops of a 10^{-1} dilution of a 7–10-day-old culture of *M. tuberculosis* in Dubos medium. When the drug is administered subcutaneously, the PD_{50} for the intravenous infection is 1.86 mg/kg as against 1.77 mg/kg for the intranasal infection.

LD_{50} of 689 mg/kg intravenously. The pharmacology of the compounds has been described by Benson *et al.* (*53*). Zieper and Lewis (*54*) administered Rimifon to a *Macacus rhesus* monkey with clinical tuberculosis and appeared to have obtained a clinical arrest, which was confirmed by post-mortem examination.

The superiority of Rimifon and Marsilid over streptomycin in mouse infections is illustrated in Table 1[3], where the efficacy of the three drugs by the subcutaneous route is compared. On this basis it is apparent that Rimifon and Marsilid are active at one thirteenth and one fifth the dose of streptomycin, respectively, in the intravenous type of infection; in the intranasal type of infection the corresponding dosage ratios are 1:56 and 1:30.

Unlike streptomycin, both Rimifon and Marsilid are

TABLE 1

Compound	Route	LD_{50} (mg/kg) *a*	Intravenous type	Intranasal type	Therapeutic ratio	
			PD_{50} (mg/kg) *b*	PD_{50} (mg/kg) *c*	*a/b*	*a/c*
Streptomycin	Subcutaneous	970	25	100	38.8	9.7
Rimifon	"	203	1.86	1.77	109	115
Marsilid	"	732	5	3.3	150	222

TABLE 2

Compound	Route	LD_{50} (mg/kg) *a*	Intravenous type	Intranasal type	Therapeutic ratio	
			PD_{50} (mg/kg) *b*	PD_{50} (mg/kg) *c*	*a/b*	*a/c*
Tibione	Per os	825	50	829	16.5	1.0
Rimifon	" "	203	4.6	6.2	44.1	32.7
Marsilid	" "	920	7.3	10.7	126	86

Similarly, the PD_{50} of Marsilid given in a medicated diet to mice with the intravenous and intranasal type of infection is 7.3 mg/kg and 10.7 mg/kg, respectively, whereas by subcutaneous administration the respective figures for the PD_{50} are 5 mg/kg and 3.3 mg/kg.

Protection of all mice, shown by the absence of characteristic lesions, was consistently achieved in an unusually low dosage range (10 mg/kg/day or less); at about twice this dosage, cultures from the lungs were negative. No comparable results could be obtained with other known antitubercular agents, such as streptomycin, PAS, and the thiosemicarbazones, even if high doses were used. Steenken and Wolinsky (*52*) observed that infected guinea pigs, which gave a positive tuberculin reaction initially, gave an almost negative test after treatment with Marsilid but remained positive after streptomycin treatment.

The acute toxicity studies in mice (*51*) show that Rimifon has an LD_{50} of 203 mg/kg orally or subcutaneously and an LD_{50} of 171 mg/kg intravenously. Marsilid, which in mice is considerably the less toxic of the two, has an oral LD_{50} of 920 mg/kg and an

practically as effective orally as they are parenterally. A comparison of the efficacy of the two, as against Tibione, given per os in mouse infections, is shown in Table 2.[3]

Preliminary clinical investigations of both drugs show them to have unusual antitubercular activity without severe toxic reactions (*50, 55, 56*). In a concluding statement, Robitzek and his co-workers (*50*) stated:

> The systemic ravages of the tuberculous process are rapidly halted; there is loss of toxicity, return of temperature to normal, recovery of appetite and remarkable weight gain. This occurs with a rapidity, a certainty and to a degree which we have never observed in other chemotherapeutic or antibiotic agents. In limited studies, we have also observed a marked effect on the local, anatomical pulmonary lesion, evidenced by some radiological changes, marked reduction in cough and expectoration in about one-third of the cases, and an apparent, at least temporary, conversion of the sputum to negative on bacteriological examination.

Conclusion. In a discussion of the chemotherapy of

[3] These tables are based on the published and unpublished work of Schnitzer and Grunberg.

tuberculosis, Florey (*4*) listed some of the features to be sought in an antitubercular agent. Among these were small molecular size with concomitant easy diffusibility to the site of infection, bactericidal rather than bacteriostatic activity in low concentrations, a slow rate of production of resistant strains, and a relative atoxicity to the host in general and to the cells of the kidney, liver, and other organs where the drug might be concentrated. At the current state of our knowledge, the isonicotinylhydrazines, as exemplified by Rimifon and Marsilid, appear to fulfill these requirements with fidelity. They are small molecules, very soluble in water, and they probably diffuse with great ease through the body tissues. They are highly active, and at certain dose levels, there is some evidence to indicate that they are bactericidal rather than bacteriostatic. From the preliminary observations of Robitzek and his co-workers (*50*), it would appear that drug resistance does not readily develop. They are relatively atoxic with a very favorable therapeutic ratio and, finally, they are effective orally and are within the economic reach of most of the civilized world.

Whether these drugs, in combination with early diagnosis and treatment, will provide the answer to the problem of tuberculosis remains to be seen. Much work must be done, and some time must elapse before we can correctly evaluate them and see them in the proper perspective. This much, however, is certain—whether with these drugs or with others—the problem will be solved; the answer will be found.

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News and Notes

Meeting of the Southwestern Division of the AAAS

THE 28th annual meeting of the Southwestern Division of the AAAS was held at the University of Colorado at Boulder, May 1–4, in conjunction with the 23rd annual meeting of the Colorado–Wyoming Academy of Science. Affiliated societies participating in the program were the Colorado–Wyoming Branch of the Society of American Bacteriologists, the Rocky Mountain Branch of the American Psychological Association, the Colorado–Wyoming Section of the American Association of Physics Teachers, and the American Association of University Professors.

The total number of registrants was 457, the largest number ever to attend any of the meetings of this division. Of the 212 papers presented, 101 dealt with the biological sciences, including psychology, 68 with the physical sciences, 24 with the social sciences, including anthropology, and 19 with engineering research.

Although the various fields of botanical science were well represented in the 37 papers presented in the Plant Science Section, special emphasis was given to pathological problems and their methods of control. The papers in systematics dealt not only with floras of the four different states in the division but also with the floras of the Caroline Islands and Japan. The ecological papers were concerned with local regions, Oregon, and Canada.

The 42 papers that zoologists contributed comprised the largest number in any one science. Ecological problems of Colorado, Wyoming, and New Mexico received the greatest attention. Results of interesting physiological research were given, including a presentation by Ed. D. Crabb of a colored sound film on the extirpation and transplantation of a tumor in a Syrian hamster.

In the joint meetings of the Psychology Section and the Rocky Mountain Branch of the American Psychological Association, the papers dealt with experimental psychology, problem solving, and clinical psychology.

In the Physics Section, 32 papers were presented, including some dealing with research on cosmic rays, astrophysics, and theoretical physics. Laboratory procedures and problems involving the teaching of physics were also considered in this section.

The research described in the 36 papers given in the Chemistry Section was distributed among practically all the important fields of chemistry, but the greater number was concerned with research in organic and biochemistry.

The social scientists met together for one general session on the "Problems of Asia" and for another on "General Education in the Social Sciences." Section meetings were also held for the presentation of research papers in the fields of history, political science, economics, and sociology. Those investigating archaeological developments in various sections of Colorado reported on their findings during the "Symposium on Colorado Prehistory," which was an important feature of the meetings of the Anthropology Section.

On the evening of the first day of the meetings, the John Wesley Powell Memorial Lecture was given by Karl P. Schmidt, chief curator of zoology of the Chicago Museum of Natural History. His subject was "The History of Animal Geography." Mr. Schmidt traced the history of theories proposed to explain present animal distribution from earliest historical records to the present. He emphasized particularly the importance of the theory of northern origin and questioned the necessity of calling upon theories of continental drift.

Following the annual dinner Friday evening in the new Masonic Building, the 200 scientists in attendance had the pleasure of listening to an illustrated lecture entitled "Into Central Australia," given by Alfred M. Bailey, of the Denver Museum of Natural History. The audience greatly enjoyed the remarkable colored movies of plants, animals, and aborigines in their native habitats, as well as the graphic description Dr. Bailey gave of the four-month expedition he led into central Australia. The object of the exploration was to collect material for the preparation of a new diorama to be placed in the Denver Museum of Natural History.

The Committee on Tours and Excursions, headed by Ralph D. Law, made arrangements for visits to various points of interest. The Cryogenics Laboratory of the U. S. Bureau of Standards at Boulder gave the visiting scientists the opportunity of inspecting the new Low Temperature Laboratory, where liquid nitrogen and liquid hydrogen are being made. A considerable number went on the scheduled auto trip to the top of Flagstaff Mountain, which overlooks Boulder, and many took advantage of the botanical excursions.

Local arrangements were under the supervision of James W. Broxon, professor of physics at the University of Colorado, who was assisted by a general committee drawn from the staffs of the fields of science represented in the AAAS. This committee, ably assisted by Hugo G. Rodeck, executive secretary of the Colorado–Wyoming Academy of Science, and Frank E. E. Germann, executive secretary-treasurer of the Southwestern Division, was responsible for the facilities and services provided.

Officers elected for next year are: president, Edna L. Johnson, University of Colorado; vice president, Paul E. Boucher, Colorado College; member of the Executive Committee, A. H. Berkman, College of Mines and Metallurgy, El Paso, Texas. Frank E. E. Germann, University of Colorado, continues as executive secretary-treasurer.

The next meeting will be held at Arizona State College, Tempe.

EDNA L. JOHNSON
Department of Biology, University of Colorado

Scientists in the News

John M. Anderson has been appointed associate professor of zoology at Cornell, following five years on the staff of the Zoology Department at Brown University.

For their contributions to telephone and other electromagnetic communications, **John Bardeen,** of the University of Illinois, and **Walter H. Brattain,** of Bell Telephone Laboratories, will be awarded Stuart Ballantine Medals by the Franklin Institute. Formal presentation of the awards will be made at Medal Day ceremonies on Oct. 15. Invention of the point contact transistor by Dr. Bardeen and Dr. Brattain grew out of their research on semiconductors, and specifically on the relatively rare element germanium, which is used in the new device.

Stanhope Bayne-Jones (brigadier general, ret.) has assumed his duties as civilian technical director of Army Medical Research, serving in the office of the Army Surgeon General. He succeeds the late **Francis G. Blake,** former dean of the Yale Medical School. Also a former dean of Yale Medical School (1935–40), Dr. Bayne-Jones will act as consultant to John R. Wood, chairman of the Army Medical Research and Development Board. Since 1947 he has been president of the Joint Administration Board of New York Hospital–Cornell Medical Center.

Doyle M. Bortner, chairman of the Department of Education and Psychology at Bates College, has been appointed professor of education and chairman of the Education Department at Hofstra College. Dr. Bortner has been at Bates College since 1948.

Everett T. Calvert has been appointed editor-in-chief of American Book Company as of Sept. 1. For the past 11 years, Dr. Calvert has been principal of Washington Elementary School, Pasadena, Calif. He will succeed **W. W. Livengood,** of the editorial staff of American Book Company since 1912 and editor-in-chief since 1931. Mr. Livengood will assume new duties as executive assistant to the president.

E. Alice Clark, Public Health Service nurse officer, has been assigned as chief nurse consultant to the Division of Venereal Disease. She will succeed **Hazel Shortal** (SCIENCE, **116,** 81 [1952]), who was recently assigned to the Institute of Inter-American Affairs. Miss Clark has been public health nurse consultant to the Kentucky State Health Department since 1950, with headquarters in Louisville.

Charles Meade Grigg, of the University of North Carolina, has been appointed assistant professor of sociology in Brown University. Dr. Grigg is conducting a summer course at North Carolina before taking up his work at Brown.

Richard R. Holmes, for the past year assistant professor of organic chemistry at Oberlin, has been appointed head of the department at the University of North Dakota.

Abelardo M. Inocentes, of Mandaluyong, Rizal, Philippines, is at the Kessler Institute for Rehabilitation to study advanced techniques of rehabilitation and reconstructive and orthopedic surgery. Dr. Inocentes will remain for a year, and his studies will include visits to other centers and hospitals in the area. Dr. Inocentes helped to establish the National Orthopedic Hospital in Rizal in 1945 and is now one of the senior orthopedic surgeons at that hospital. He has served on the staffs of the Maternity and Children's Hospital in Manila, at the Bureau of Prisons Hospital, and the Manila Central Hospital.

As the new Hearst Research Laboratories at the National Jewish Hospital in Denver near completion, the appointment of **Gardner Middlebrook** as director of research and laboratories has been announced. Dr. Middlebrook leaves his post as associate in the Department of Pathology and Microbiology at the Rockefeller Institute for Medical Research to succeed **Harry J. Corper,** who has retired after 32 years as the Denver institution's research head.

Bernard L. Miller has joined the staff of St. Joseph's College as associate professor of physics. He has been with the research division of the Burroughs Adding Machine Company and was previously in charge of the development of the linear electron accelerator at the Bartol Foundation of the Franklin Institute.

Herbert Milwit has assumed command of the Engineer Research and Development Laboratories, Fort Belvoir, Va. He was formerly with the Photographic and Survey Section of the Joint Intelligence Group of the Joint Staff, and since August 1951 he has been a student at the Industrial College of the Armed Forces.

A. G. Norman, biochemist and division chief, Chemical Corps Biological Laboratories, Camp Detrick, Md., since 1946, has resigned to accept a research position at the University of Michigan, in charge of a project on plant nutrition supported by the Phoenix Memorial Fund.

Students and colleagues gave a dinner in honor of **Charles J. Pieper,** chairman of the department of Science Education at New York University, who will retire at the close of the summer session after 24 years of service with the university.

Harry M. Rose has been appointed chairman of the Department of Microbiology at Columbia University's College of Physicians and Surgeons. Dr. Rose has also been designated John E. Borne professor of medical and surgical research. He is secretary of the Medical Division of the Society of American Bacteriologists and a member of the Armed Forces Epidemiological Board.

Laurence H. Snyder, of the University of Oklahoma, and a member of the AAAS Executive Committee, has been designated to represent the officers and Executive Committee of the Association at the Third Alaskan Science Conference, Mount Mc-

Kinley National Park, Sept. 22–27. The conference is also the second annual meeting of the Alaska Division of the AAAS.

Carl Tiedcke, director of the Laboratory of Microchemistry, Teaneck, N. J., is visiting Turkey at the invitation of the University of Istanbul for conferences and lectures on the application of modern microchemical methods to hygiene, sanitation, soil chemistry, and metallurgy.

Ernest S. Tierkel, veterinarian in charge of rabies control activities for the Communicable Disease Center, Atlanta, has left for a three months' tour of duty in Europe and Asia under the auspices of WHO. Before beginning his consultations with various governments, he taught at a 30-nation rabies conference July 14–28 at the Pasteur Institute, Coonoor, Madras, India. Nations that have asked for his assistance in rabies control this year include Burma, Thailand, Indonesia, Greece, Spain, and the western sector of Berlin. Dr. Tierkel is assistant chief of the Veterinary Public Health Section of the Communicable Disease Center, USPHS.

Alfred N. Watson has been appointed research associate in the School of Industrial Management at Massachusetts Institute of Technology. Dr. Watson was previously assistant treasurer of the Curtis Publishing Co. and president of National Analysts, Inc., Curtis subsidiary for market research. In addition to his duties at MIT, he will be associated with Arthur D. Little, Inc., where he will be engaged in the application of operations-research techniques to the study and improvement of business and industrial operations.

James Westfield, a mining engineer with 24 years of service in the Bureau of Mines, has been made chief of the Health and Safety Division. He assumes the post held by **J. J. Forbes** until his appointment as director of the Bureau of Mines last November. Mr. Westfield worked in coal and metal mines in Utah from 1921 until he joined the Bureau of Mines in 1928. From first-aid miner, he advanced to chief of the Accident Prevention and Health Division of the bureau's Region VIII, with headquarters at Pittsburgh, Pa., in 1950.

On July 14, the College of Physicians of Philadelphia awarded the Alvarenga Prize for 1952 to **Norbert Wiener,** professor of mathematics, Massachusetts Institute of Technology, for his contribution to the field of cybernetics. The Alvarenga Prize was established by the will of Pedro Francisco DaCosta Alvarenga of Lisbon, an associate fellow of the College of Physicians, to be awarded annually on the anniversary of the death of the testator, July 14, 1883.

Frederick Wyatt has accepted an appointment as chief of the Psychological Clinic of the Institute for Human Adjustment at the University of Michigan. He has also been appointed associate professor in the Department of Psychology.

Education

Columbia University has added two organic chemists to the staff of the Department of Chemistry: Cheves Walling will become professor of chemistry immediately, and Gilbert Stork will become associate professor on Feb. 1.

More than 100 college and high school mathematics teachers are attending a 10-day institute at **Duke University,** beginning this week. General theme of this year's institute, which was founded 12 years ago by W. W. Rankin, is "Mathematics at Work."

The **University of Illinois** has established an Institute for Research on Exceptional Children which will provide opportunities for training research workers and improve the effectiveness of the work of both public and private agencies. Director of the new institute will be Samuel A. Kirk, professor of education. An advisory committee representing the university, and the state departments of Public Welfare and of Public Instruction will be named to suggest guiding policies.

North Dakota Agricultural College has appointed Parker M. Green, of General Motors Institute, professor of mechanical engineering. Increased enrollment has necessitated an expansion of the Engineering Department.

George A. Wolf, Jr., has been appointed dean of the **University of Vermont** College of Medicine, succeeding William E. Brown, who retired June 30. B. F. Clark has been appointed assistant professor of obstetrics and gynecology, and H. T. Guare, assistant professor of radiology.

Grants and Fellowships

The **Birtcher Corporation,** of Los Angeles, has provided a grant of $3500 to the College of Medical Evangelists' School of Medicine for research on the biological effects of ultrasonics. Charles E. Winter, of the Bacteriology Department, and Robert W. Woods, assistant professor of biophysics, are working on the project.

Commonwealth Fund British Fellowships for 1952–53 will enable 32 British scholars to come to the U. S. to study and do research in universities ranging from New England to the Far West. Among them are: Laurence J. Cohen, of Balliol College, Oxford, who will study mathematical logic at Princeton and Harvard; Hugh E. Huxley, of Christ's College, Cambridge, who will investigate the molecular structure of muscle and the mechanism of muscular contraction at MIT; Ronald B. Thompson, of King's College, Durham, who will study hematology at the University of Utah College of Medicine; and Vivian Vale, of Jesus College, Cambridge, will survey American labor history during the period 1859–79, initially at the University of Wisconsin.

Eastman Kodak Company is offering 14 fellowships

for advanced study in chemistry, chemical engineering, and in physics, and Tennessee Eastman Company is offering five additional fellowships to educational institutions in the Southeast. Each award provides $1400 plus an allowance for tuition and fees, and the fellow is selected by his university in the last year of study for his doctorate. Catholic University, Illinois Tech, MIT, Ohio State, Princeton, Northwestern, Stanford, Cornell, Harvard, and the universities of Rochester, Texas, and Wisconsin are the recipients of the 1952–53 awards.

Rome Cable Foundation, Inc., has established the Herbert Thomas Dyett Scholarships for study in the fields of science, engineering, or business administration, in honor of the founder and chairman of the board of Rome Cable Corporation. Five graduates of the Rome (N. Y.) Free Academy were the first recipients. Three of them—Leon F. Albrecht, Jr., Joseph E. Carrier, and John E. Clark—will study at Cornell; Robert C. Kain will attend Rennselaer Polytechnic, and Carl J. Link, Jr., will enter Purdue.

Meetings and Elections

The **Advisory Group of the Armed Forces Medical Library,** composed of five civilians and four Armed Forces officers, replaces the Association of Consultants to the Army Medical Library. W. C. Davison, former president of the association and chairman of the Executive Committee, has been appointed to the new group. The other civilian members are Richard Shryock, Basil G. Bibby, Janet Doe, and Karl F. Meyer.

At the last meeting of the **AAAS Executive Committee,** the following organizations were granted affiliated status: American Association of Clinical Chemists, Inc. (Section C), American Ethnological Society, Inc. (Section H), Society of Exploration Geophysicists (Section E), the Southern Association of Science and Industry (Section P), and the Hawaiian Academy of Science.

The eighth general assembly of the **International Geographical Union** and the seventeenth **International Geographical Congress** are being held in Washington, D. C., Aug. 8–15. Other geographic organizations scheduled meetings which preceded the main international program—among them, the third Pan American Consultation on Geography, July 25–Aug. 4, in Washington; the 100th anniversary celebration of the American Geographical Society, Aug. 4–6, in New York; the annual meetings of the Association of American Geographers and of the National Council of Geography Teachers, Aug. 6–7, in Washington.

At the sessions in Washington two general symposia are planned—one dealing with tropical Africa, and the other with the world food supply. Sectional meetings have been scheduled for the presentation of papers on Geomorphology; Climatology; Hydrography; Demography and Cultural Geography; Urban and Rural Settlement; Resources, Agriculture, and Industry; Trade and Transportation; Cartography; Historical and Political Geography; Biogeography; Regional Geography; and Teaching of Geography. In addition, commissions of the International Geographical Union have arranged sessions on Geographical Utilization of Aerial Photographs; Agrarian Geography; Bibliography of Ancient Maps; Industrial Ports; International Map of the World; Medical Geography; Periglacial Morphology; Population; Regional Planning; Soil Erosion; Terraces; and Inventory of World Land Use. The evening programs include a miscellany of receptions, entertainment, and lectures, as well as the official banquet on Aug. 13, at which Hans W: son Ahlmann will deliver the third Isaiah Bowman memorial lecture.

Excursions preceded the meeting in Washington, and others will follow. A New England excursion under the leadership of John H. Thompson and Edward C. Higbee was scheduled for July 26–Aug. 3; a tour of the industrial cities of the East and Midwest was arranged for July 26–Aug. 4 and will be repeated Aug. 16–25, under the leadership of Harold M. Mayer and Lester E. Klimm; a Southern excursion is scheduled for Aug. 16–26, with Eugene Mather and John Fraser Hart as leaders; and there is the inevitable transcontinental excursion, Aug. 16–Sept. 11, under the guidance of William E. Powers and Richard F. Logan.

George B. Cressey, of Syracuse University, has been president of the International Geographical Union since its last meeting, and he will give one of the principal addresses, on "Land for 2.4 Billion Neighbors," at the sessions in Washington. The U. S. National Committee, which has had general charge of arrangements, has been directed by Wallace W. Atwood, Jr., chairman, who is one of the AAAS representatives at the Congress. Other official AAAS representatives are Detlev W. Bronk, Paul B. Sears, and Howard A. Meyerhoff. Samuel Van Valkenburg has served as chairman of the congress program committee, and Clyde F. Kohn as chairman of the committee on excursions. The National Academy of Sciences and the National Research Council will act as official hosts, and the meetings will be held in the Hotel Statler.

Miscellaneous

A five-year research program on plate efficiencies in fractionating towers, a cooperative project between the **American Institute of Chemical Engineers** and 25 chemical, petroleum, and engineering organizations, will be carried out at the universities of Delaware and Michigan and at the Polytechnic Institute of Brooklyn. The work on the initial project, which is supported by $64,000 in contributions for the first year, will be under the supervision of Brymer Williams (Michigan), J. A. Gerster (Delaware), and Ju Chin Chu (Brooklyn).

Recent visitors at the **Eastern Regional Research Laboratory,** ARA, Philadelphia, included Gunnar

Baalsrud, E. and O. Collett and Co., Oslo; Franco Testore and Enzo M. Bona, International Organization for Standardization, Torino, Italy; Joseph Meyer, president, Ceres de Mexico, Yucatán; and Pierre Desnuelle, Faculty of Sciences, Marseille.

At the request of the Bureau of the Budget the **National Science Foundation** is compiling statistical and fiscal information for 1951 and 1952 from federal agencies supporting scientific research and development programs by grant or contract with educational and other nonprofit institutions. The final report is expected to be available before Jan. 1.

The **New York Zoological Park** has revived the title of director, and John Tee-Van has been appointed to the position. Leonard J. Goss has been made assistant director and will continue as veterinarian. Lee S. Crandall, general curator, retired on July 31, but will maintain an office at the park and will be engaged in the preparation of books on the care, feeding, maintenance, and exhibition of wild animals in captivity, based on his 44 years of experience with the Bronx Zoo. Robert M. McClung has been named acting curator of mammals and birds. William Beebe has become director emeritus of the Department of Tropical Research, and Jocelyn Crane has been made assistant director. Dr. Beebe will return to the field station in Trinidad this fall to resume his research projects there.

The **Society of Protozoologists** is establishing a center of information for available cultures of free-living and parasitic protozoa and algal flagellates maintained in the U. S. and other countries. Scientists who are willing to cooperate in the formation of this reference list and who are willing to send cultures to other investigators should secure from the Committee on Culture of Protozoa a data card for each species maintained in their laboratories. Upon payment of a nominal fee, photostatic copies of the master data cards will be furnished. Chairman of the committee is L. Provasoli, Haskins Laboratories, 305 E. 43rd St., New York 17.

Recent Deaths

Fred R. Adams (80), dentist, Brooklyn, July 17; **Michael G. Albert** (51), radiologist, New York, June 21; **Charles E. Basso** (51), engineer, La Posta, Bolivia, July 17; **Walter A. Bastedo** (79), pharmacologist, New York, July 21; **Walter Van Dyke Bingham** (72), psychologist, Washington, D. C., July 8; **J. Harold Brownback** (54), biologist, Philadelphia, July 13; **James W. Buchanan** (64), director of research, Allan Hancock Foundation, Los Angeles, June 27; **Thomas S. Burns** (61), hydraulic engineer, Athens, July 7; **Hugh Cairns** (56), brain surgeon, Oxford, Eng., July 18; **Harry E. Clifford** (86), electrical engineer, Newton, Mass., July 7; **John M. Cunningham** (75), medical educator, Indianapolis, June 29; **Wilbur B. Dexter** (60), research chemist, Cleveland, July 13; **Horace A. Du Bois** (52), research chemist, Neenah, Wis., July 18; **Virgilio Ducceschi** (81), physiologist, Padua, Italy, June 21.

William J. Elser (79), pathologist, Kent, Conn., July 6; **Norman S. Essig** (82), dentist, St. Michael's, Md., July 2; **H. T. Fernald** (86), entomologist, Winter Park, Fla., July 15; **Alfred E. Forstall** (88), consulting engineer, Montclair, N. J., July 2; **Edwin H. Fox** (60), engineer, Cincinnati, July 13; **Erik Freitag** (68), engineer, Burlingame, Calif., June 28; **Augustin Frigon** (64), director of planning and research, Canadian Broadcasting Corporation, Sixteen Island Lake, Que., July 9; **Hoyt S. Gale** (76), geologist, Los Angeles, July 6; **Leo I. Hargadon** (71), librarian emeritus, Fordham University, New York, July 16; **Mary I. Hussey** (76), linguist, Andover, Mass., June 20; **Merritte W. Ireland** (85), former Army Surgeon General, Washington, D. C., July 5; **Henry E. Jacoby** (71), chemical engineer, Yonkers, N. Y., July 13; **Roland G. Kent** (75), philologist, Philadelphia, June 27; **Frederick H. Lane** (69), chemical engineer, Sarasota, Fla., July 12.

Warren B. Mack (56), of State College, Pa., horticulturist, Philadelphia, July 6; **Frank C. Parker** (74), eye surgeon, Norristown, Pa., July 2; **John C. Penn** (70), civil engineer, Dalton Manor, Ill., July 20; **Clara N. Perine** (85), anatomist and biologist, Primos, Pa., July 16; **Wilhelmina A. Ragland** (71), obstetrician, New York, June 27; **Warwick L. Scott** (60), archaeologist, London, June 19; **Victor Shevkunenko** (80), Lt. Gen. of Medical Services, USSR, Moscow, July 5; **Howard J. Shore** (70), biochemist, Fort Dodge, Ia., June 19; **George H. Smith** (66), immunologist, New Haven, Conn., July 7; **Bernard H. Smith** (73), of Brooklyn, industrial chemist, Stockholm, N. J., July 4; **Urbana Spink** (76), brain specialist, Indianapolis, July 7; **A. Monroe Stowe** (69), educator, Washington, D. C., July 16; **Nikolai Strazhesko** (—), surgeon, Moscow, June 28; **Freeman P. Stroup** (83), organic chemist, Oil City, Pa., July 19; **Allyn C. Swinnerton** (54), geologist, secretary AAAS Section E, 1941–44, Yellow Springs, O., July 6.

Norman S. Taber (60), economist, Orange, N. J., July 15; **Harris Taylor** (87), educator, New York, July 14; **Bayard T. Thompson** (73), entomologist, Berkeley Heights, N. J., June 27; **Phineas C. Thompson** (—), geologist, New York, June 20; **T. Kennard Thomson** (88), civil engineer, Yonkers, N. Y., July 1; **Louisa P. Tingley** (83), physician, Boston, July 16; **Homer B. Vanderblue** (63), economist, Evanston, Ill., July 12; **James B. Ward** (38), geologist, Port-au-Prince, July 9; **Elisabeth M. Weil** (—), of Pearl River, N. Y., dermatologist, New York, July 8; **Olin West** (77), physician, Nashville, Tenn., June 19; **Thomas H. White** (83), horticulturist, College Park, Md., July 5; **Moshe Wilbushewitz** (83), engineer, Tel Aviv, July 15; **George P. Winship** (80), bibliographer, Dover, Mass., June 22; **Abraham Wolfson** (58), orthodontist, East Orange, N. J., July 18; **Franklin P. Wood** (77), electrical engineer, Washington, D. C., July 18; **George C. Yeager** (74), physician, Pitman, N. J., July 7.

Technical Papers

Low Energy Counting with a New Liquid Scintillation Solute[1]

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Scintillation studies involving low energy β-emitters such as C^{14} and H^3 require serious consideration of factors rarely encountered in high energy counting.

Conventional photomultipliers with low work function Cs-Sb cathodes (*1, 2*) give large counting rates of dark current in the low amplitude pulse region. Furthermore, Cs-Sb and Ag-Mg (*1*) dynodes are known to emit light on electron bombardment, some of which may not only produce a small amount of regeneration in the originating tube but may also pass over into a coincidence-arranged second tube. These practically coincident pulse phenomena can be referred to as "light dark current."

Our program on C^{14} and H^3 scintillation counting has made use of both coincidence circuitry and refrigeration to decrease dark current. Operation of the photomultipliers and scintillator at 0° C and below does not allow the use of the relatively insoluble *p*-terphenyl (*3*) (I), and therefore has forced us to investigate new and more soluble solutes.

I II

2, 5-Diphenyloxazole (*4*) (II) has a solubility of 300 g/liter in toluene at room temperature, over forty times as great as *p*-terphenyl. As judged from its variation of RCA 5819 anode current production vs. concentration, 3 g/liter in toluene makes a suitable solution for counting.

This solution will absorb, per centimeter of path through it, more than 10% of light with wavelength less than 368 mμ. It gives a radium-excited scintillation spectrum ranging from 340 to 460 mμ, with maximum intensity at 380 mμ. Similar spectral values for 0.5% *p*-terphenyl in toluene are a range of 320–450 mμ and a maximum of 352 mμ.

The counting apparatus employs a supported removable Pyrex cell viewed by 2 RCA 5819 tubes selected for high signal-to-noise ratio and oriented at 90° to each other in a horizontal plane. This assembly, together with subminiature preamplifiers and 4 in. of iron shielding, was placed in a 6 cu ft refrigerator. The separate outputs were fed into wide band amplifiers and then into fast discriminators with delay line shaped outputs of 0.2 μsec duration. A separate output from one of the amplifiers was taken into a high level discriminator with a pulse width of 4 μsec. The three discriminator outputs were combined in a fast coincidence-anticoincidence circuit, giving passage of low level coincident pulses and rejection of pulses originating in the scintillator of amplitude high enough to be passed by the high level discriminator.

With 30 ml of 0.3% II in toluene and a total amplification of 2500, 35% of the disintegrations from dissolved C^{14}-benzoic acid are recorded as pulses of amplitude between 0.5 and 15 v. Counts/min of total noise include 1–2 of dark current, 20–25 of "light dark current," and 40–60 of radiation background. Use of the dioxane-water solvent and *p*-terphenyl described by Farmer and Berstein (*5*) gave only 7% efficiency with this instrument.

Comparison of compounds for their quenching action on the toluene solution of II gave the order: piperidine > phenol >> pyridine >> cyclohexanone > chlorobenzene >> acetic acid >> chlorocyclohexane = cyclohexanol > cyclohexane > toluene at 10 mole per cent.

A detailed single and mixed solvent study on this compound (II) together with similar studies on more than thirty new solutes will be published shortly.

[1] Work done under the auspices of the Atomic Energy Commission.

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Body Build and Body Composition

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Sheldon's system of somatotyping was originally proposed as a means for describing the over-all body "type," conceived as a fairly fixed, "constitutional" characteristic (*1*). However, it has been clearly shown (*2*) that the somatotype ratings are markedly affected by changes in nutritional status and, in fact, may be considered as partial measures of nutriture. Although this may have eliminated the supposed virtue of the system as providing a permanent (constitutional) index, its possibilities as a measure of nutriture deserve to be critically examined.

Stuart and Sobel (*3*) noted, in passing and without quantitative documentation, the positive relationship between endomorphy ratings and fatness. An individual predominantly endomorphic in his body type has a heavy *panniculus adiposus*, whereas an ecto-

TABLE 1

COEFFICIENTS OF CORRELATION (r) BETWEEN RATINGS OF SOMATOTYPE COMPONENTS AND SPECIFIC GRAVITY. $N = 62$ PAIRS OF VALUES FOR LASKER AND THE HARVARD GROUP

Somatotype component	Lasker	Harvard group
Endomorphy	−.716	−.637
Ectomorphy	+.582	+.601

morphic individual will tend to have a light or thin fold of subcutaneous tissues. Dupertuis *et al.* (*4*) obtained a high negative correlation between specific gravity and the endomorphy ratings in a group of 81 healthy male subjects, selected to include representatives of the extremes of body build. Round and soft, "fat" individuals had a low body density, whereas "lean" people tended to have higher body density. The following coefficients of product-moment correlation were obtained between specific gravity and the ratings of somatotype components: for endomorphy, −0.853; for mesomorphy, +0.167; and for ectomorphy, +0.369.

The present communication is concerned with the relationship between somatotype ratings and specific gravity in a group of individuals studied on two occasions. The subjects were 31 young men, examined under control conditions and after 24 weeks of semi-starvation associated with a loss of one quarter of body weight and a marked loss of body fat (*5*). The men were somatotyped, on the basis of photographs, by Gabriel W. Lasker, Department of Anatomy, Wayne University, and by a group directed by James M. Andrews, IV, at Harvard University (*2*).[1] The ratings were carried out independently and without knowledge of the subject's nutritional status. Both sets of ratings indicated a marked mean decrement in endomorphy, slight decrease in mesomorphy, and a marked increase in ectomorphy. The coefficients of correlation between the two sets of ratings of the three components of the somatotype (endomorphy, mesomorphy, and ectomorphy) were +0.856, +0.622, and +0.862, respectively.

[1] The authors alone are responsible for the utilization and interpretation of the data in this communication.

The coefficients of correlation between the somatotype ratings and specific gravity, with the volume of the body determined by underwater weighing, are presented in Table 1. The correlation is statistically highly significant for endomorphy (negative r) and ectomorphy (positive r). There are factors inherent in the sampling and in the method of measurement which tend to increase the correlation (a marked heterogeneity of the nutritional status), as well as to decrease it (inaccuracy of specific gravity determinations resulting from the use of average correction for residual air). Nevertheless the values are in essential agreement with Dupertuis' observations except for mesomorphy ratings, which yielded low negative values in our material and low positive r values in the sample of Navy men.

Table 2 contains predicted values of specific gravity (and estimated body fat [*6*]) corresponding to different ratings of endomorphy and ectomorphy. This is to indicate in a more concrete way the meaning of the correlation coefficients.

It is not our intention, however, to suggest using somatotype ratings for estimation of body fat. This appears to be a devious and inefficient route, except under special conditions in which direct measurements on the living man were not or could not be made. For these conditions a system of ratings and measurements (based on photographs) is needed that is more directly focused on the evaluation of individual differences in the basic anatomical components of the body than are Sheldon's "components" of the body type. It is the estimation of the absolute and relative amount of fat—which accounts for the largest part of the differences among adult individuals—of muscles, and of bones, which is the principal concern of nutritionally oriented anthropometry.

Elsewhere (*7*) equations were developed for predicting total fatness on the basis of measurements of skinfolds, varying in thickness as a result of different amounts of subcutaneous adipose tissues. This is a simple, objective, and rapid procedure. For younger men the coefficient of multiple correlation between

TABLE 2

PREDICTED VALUES OF SPECIFIC GRAVITY AND BODY FAT FOR YOUNG MEN (AV AGE, 26 YEARS) RATED WITH REFERENCE TO SOMATOTYPE COMPONENTS. THE PREDICTION EQUATION WAS BASED ON COMBINED LASKER AND HARVARD RATINGS ($N = 124$)

	Endomorphy ratings						
	1	2	3	4	5	6	7
Sp gr	1.0938	1.0857	1.0776	1.0695	1.0614	1.0533	1.0452
Fat (%)	2.8	6.6	10.5	14.4	18.3	22.3	26.4
	Ectomorphy ratings						
	1	2	3	4	5	6	7
Sp gr	1.0598	1.0659	1.0720	1.0780	1.0841	1.0902	1.0962
Fat (%)	19.1	16.0	13.1	10.3	7.4	4.7	1.9

specific gravity and skinfolds was 0.871, for older men 0.743, using skinfolds measured at 3 and 4 points of the body surface, respectively. The standard errors of estimate of the specific gravity are 0.0072 and 0.0086.

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Specific Volumes of Proteins and the Relationship to their Amino Acid Contents

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The specific volume of a protein is essential for calculating its molecular weight in solution and for relating the composition of a protein crystal to its density. Values for specific volumes are obtained experimentally from density measurements. Cohn and Edsall (*1*) have, however, described a method for calculating the specific volume of a protein from its amino acid composition, the volume of the protein molecule being considered to be the sum of the volumes of its component groups or atoms. At the time of publication of this method for calculating specific volumes of proteins from their amino acid compositions, the data on the amino acid composition of proteins were incomplete and unreliable. During the past ten years, new methods, such as the use of isotopes, bacteria, and chromatography, in the determination of amino acids have led to reliable and fairly complete amino acid analysis on a large number of proteins. It became of importance and interest, therefore, to test the method for calculating specific volumes of proteins using recent quantitative amino acid composition data. Values obtained for the specific volume of a number of proteins calculated from their amino acid composition are compared in Table 1 with the observed values obtained by density measurements. It may be noted that in most cases the values calculated from the amino acid composition are in excellent agreement with the observed values. The differences between the observed and calculated values for the last three proteins in the table are greater than might be expected in view of the other results and suggest that the amino acid composition and specific volume for these three proteins be redetermined.

The method for calculating a specific volume from the amino acid composition neglects electrostriction that is due to charged groups in the protein molecule; consequently, it might be expected that the calculated value for the specific volume would be higher than that observed. Cohn and Edsall (*1*) calculated that the value of the specific volume of egg albumin in solution would be reduced by 2.4% because of electrostriction. The value for electrostriction in other proteins would vary slightly owing to the number of charged groups in the molecule. Linderstrøm-Lang (*21*) observed that the initial enzymic hydrolysis of a protein involves a large change in volume per mole of peptide bond split (−50 cc). The preponderance of the peptide bonds in the protein, however, was found to give the normal contraction in volume when split (−20 cc); accordingly, the total effect of this volume factor on the specific volume of the protein would not be expected to be large. The excellent agreement between the calculated and observed values for the specific volumes of proteins may be due in part, therefore, to a compensation of variables.

The fact that the values for the volumes of proteins obtained by these two methods agree for such a wide variety of proteins is considered to be good evidence that the volume of a protein molecule in solution is essentially equal to the sum of the volumes of its component groups and that the method of Cohn and Edsall for calculating specific volumes is reliable.

TABLE 1

Specific Volume of Proteins

Protein	Sp vol observed* (cc/g)	Sp vol calcd from amino acid composition† (cc/g)
Silk fibroin (suspended in H_2O)	0.701 (*2*)	0.689 (*3*)
Ribonuclease	.709 (*4*)	.703 (*3*)
Wool (suspended in H_2O)	.716 (*5*)	.712 (*3*)
Lysozyme	.722 (*6*)	.717 (*7*)
Fibrinogen (human)	.725 (*8*)	.723 (*3*)
α-Casein	.728 (*9*)	.725 (*9*)
Chymotrypsinogen	.73 (*10*)	.734 (*3*)
Casein (unfractionated)	.731 (*9*)	.731 (*9*)
Serum albumin (bovine)	.734 (*11*)	.734 (*12*)
Insulin (Zn)	.735 (*13*)	.724 (*3*)‡
D-glyceraldehyde phosphate dehydrogenase	.737 (*11*)	.743 (*11*)
Aldolase	.740 (*11*)	.743 (*11*)
β-Casein	.741 (*9*)	.743 (*9*)
Ovalbumin	.745 (*14*)	.738 (*3*)
Hemoglobin (horse)	.749 (*15*)	.741 (*3*)§
β-Lactoglobulin	.751 (*16*)	.746 (*17*)
Botulinus toxin	.75 (*18*)	.736 (*18*)
Gelatin	.682 (*19*)	.707 (*3*)
Edestin	0.744 (*20*)	0.719 (*3*)

* These values were determined at 20° C. or close thereto.
† With the exception of references (*9*), (*11*), and (*18*), the specific volume values have been calculated from the amino acid compositions given in the cited reference. A value of 0.63 cc was used for the volume of the cystine residue instead of 0.61 cc, as given in Cohn and Edsall (*1*).
‡ The specific volume of zinc is not included.
§ The specific volume of hemin is not included.

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

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A Note on the Phosphorescence of Proteins

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As the literature on the fluorescence and phosphorescence of proteins is scanty, and since it is of interest to know more about this subject and its relation to protein denaturation, an investigation of the visible light emitted by proteins under ultraviolet excitation has been carried out.

Wels (*1*) and Vlés (*2*) reported that a blue fluorescence was observed when proteins were irradiated with ultraviolet light at room temperature. The intensity of the fluorescence (which is not strong) depends on the pH and the oxygen content of the solution and on the irradiation time. It can be excited by many different wavelengths of the ultraviolet region.

With compact animal materials such as nails, tendons, and cartilage, a distinct blue phosphorescence which lasts about 0.2 sec at room temperature has been reported (*3, 4*). The globular proteins and noncompact body materials such as muscle did not exhibit this phosphorescence.

We have found that many proteins emit a brilliant blue phosphorescence at low temperatures. However, no fluorescence in the visible range has been observed in any of our experiments.

The proteins used in this study were bovine serum albumin, egg albumin, gelatin, human γ_2-globulin, zein, human fibrinogen, silk fibroin, and keratin (human nail). Material containing protein such as bacteria (*Escherichia coli*), commercial yeast, "Witte" peptone, agar, and dehydrated beef muscle show the same phosphorescent properties as the individual proteins. The emission was observed with solid protein, with suspensions, and with solutions.

In order to find out which groups in the proteins are active, 18 amino acids were investigated. Of these, only the 3 common aromatic amino acids (tyrosine, tryptophane, and phenylalanine) gave indications of characteristic emissions. However, the remaining 15, including histidine, showed weak blue emissions which had the characteristics of those from tyrosine and tryptophane. Since it was found that as little as 10^{-9} g of tyrosine gives a discernible blue phosphorescence, it is our opinion that the blue emissions of these 15 are caused by trace amounts of the aromatic amino acids. Indeed, it seems that phosphorescence is a sensitive detector of certain impurities.

These experiments, unless stated otherwise, were carried out at the temperature of liquid nitrogen (77° K). A General Electric AH-6 mercury-vapor arc was used as the source of ultraviolet light. For the kinetic studies, an RCA 5819 multiplier phototube and either an oscillograph or a galvanometer have been employed, depending on the rate of decay. The spectra were determined with a Hilger constant deviation spectrograph and Eastman Kodak spectrographic plates.

At any particular pH, there are at least two exponential decay emissions from the majority of the proteins. Results with the oscillograph, although complicated, indicate that the lifetimes[3] are about 3 sec. Some experiments at the temperature of dry ice (193° K) were less complicated, and it was found possible to prove the monomolecular nature of the decay, the semilog plots being consistent and the decay constants being reproducible at that temperature.

The amino acid tryptophane has a bluish-white phosphorescence with a lifetime of about 3 sec at all pH values. The phosphorescence of tyrosine is brilliant and deep blue; it has a lifetime of about 3 sec in neutral and acid solutions, whereas the lifetime in alkaline media is 0.9 sec. The emission of phenylalanine also seems to be bluish-white, but its lifetime is much shorter, probably being less than 0.1 sec.

The visible spectrum of the protein phosphorescence is dependent on the pH, which fact may be attributed to the association of protons to the aromatic amino acids (*5*). In Table 1, some of the features of protein phosphorescence in alkaline media are pre-

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[2] We gratefully acknowledge the donation of the human γ_2-globulin by J. W. Williams, of the University of Wisconsin, and also the fibrinogen and the bacteria culture by H. A. Scheraga and J. C. White, respectively, of Cornell University. Guy C. Bell, Jr., aided in some of the experimental work.

[3] The mean lifetime of an exponential decay is that amount of time necessary for the phosphorescence to fall to $1/e$ of its initial intensity.

sented. The relative intensities seem to be independent of the protein, for similar spectra were obtained with bovine serum albumin, egg albumin, and trypsin. The results in acid solution were less consistent, with the main maximum appearing at 4170 A. The phosphorescence spectra of tyrosine and tryptophane in alkaline media have been found to lie in the same wavelength region as the protein phosphorescence.

TABLE 1

PROTEIN PHOSPHORESCENCE SPECTRUM FEATURES

Wavelength (A)	Feature
4020	Marked shoulder
4180	Minor maximum
4200	Small minimum
4250	Small shoulder
4400	Broad, intense maximum
~ 4800	Cutoff

The exponential-decay phosphorescence of proteins can be attributed to tyrosine, tryptophane, and possibly phenylalanine. Since the emission is not sensitive to temperature changes, it appears to be an electronic transition. A long series of investigations was carried out by G. N. Lewis and his group on just such transitions of aromatic compounds. As the results here parallel theirs, it is assumed that the observed transitions are of the same type. The nature of this phosphorescence was reviewed by Kasha (*6*); Nauman (*5*) has studied the spectra, and McClure (*7*) investigated the transition rates. Their work indicates that the excited phosphorescent state is the lowest-lying triplet level.

A protein phosphorescence of very long duration has been observed along with the exponential-decay phosphorescence, but the mechanism is quite different. The long-lifetime emission is highly sensitive to temperature increases, and proceeds so rapidly at the dry ice temperature that it is not observed. According to Linschitz (*8*), the spectrum probably is the same as that of the exponential-decay phosphorescence. The presence or absence of this emission is a sensitive function of the pH, for it is strong in alkaline media but absent in acid media. It has been possible to study the rate of decay of the long-lifetime phosphorescence, and a report has been made elsewhere on the observed rate law and the associated mechanism (*9*).

The long-lifetime phosphorescence can be attributed to certain forms of the aromatic amino acids. Phenylalanine does not have a long-lifetime emission; tryptophane does in neutral and alkaline media, and tyrosine has this phosphorescence only in alkaline media. Further study of this phenomenon with many organic compounds has shown that the anilinium ion and free phenol forms are not active, whereas the free aniline base and phenolate ion forms are active, at least under the present conditions.

A complete description of the long-lifetime phosphorescence is not pertinent here, but a brief mention of its nature will be given, for we feel that it is related to the denaturation of proteins by ultraviolet light. The molecule absorbs a quantum of light and an electron is photo-ejected into the surrounding solid. At 77° K, the rate of return, which we believe to be diffusion-controlled, is slow; the phosphorescence occurs when the electron returns to the protein.

Harris (*10*) observed that most proteins take up oxygen when irradiated with light from the mercury-vapor arc, and that tyrosine and tryptophane absorb oxygen at a rapid rate. Gelatin (which contains little tyrosine and no tryptophane, and whose phosphorescence is much weaker than that of most other proteins) and most amino acids do not absorb oxygen.

Whether the oxygen reacts with the dissociated electron, with the protein which has lost an electron, or with the protein containing a group which has been excited into the triplet state is a question which cannot be answered with present information. It does seem quite probable that the intermediates in phosphorescence play a large part in the photo-oxidation of proteins and in their photodenaturation. Further, tyrosine and tryptophane are undoubtedly the main contributors to protein phosphorescence, both of the exponential and of the long-lifetime type.

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The Presence of Toxins other than DDT in the Blood of DDT-poisoned Roaches[1]

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It has been reported by Bot (*1*) that roaches (*Periplaneta americana* L.) in the prostrate stage of poisoning after topical application of DDT may contain sufficient DDT in their blood to produce typical DDT-poisoning symptoms and death in flies (*Calliphora erythrocephala* Meig.) injected with a volume of 20 µl of such blood. Our first attempts (*2*) to duplicate the work of Bot resulted in failure, presumably because we bled roaches too early in the prostrate stage of poisoning or allowed them to approach too close to death. We have since been able to obtain samples of blood from prostrate roaches which produce the effects described by Bot, but we have not been able consistently to obtain samples with a level of toxicity that

[1] Supported by funds from the Rockefeller Foundation.
[2] We wish to thank C. Ladd Prosser for his helpful advice and loan of equipment.

will produce indisputable symptoms. Part of the difficulty arises from the fact that the most toxic samples are sufficient to produce definite symptoms only when injected in volumes approaching the maximum that the housefly or the flesh fly (*Sarcophaga crassipalpis* Macq.) will tolerate if injected with blood from normal roaches.

We have chemically analyzed blood samples taken from DDT-poisoned roaches by the Schechter-Haller (*3*) method and find that they may contain from less than 1 to as much as 15 ppm DDT. These analyses were made using a microadaptation of the Schechter-Haller method, where 0.2 μg DDT can be determined accurately and amounts down to 0.05 μg detected. The method of application of DDT to the roaches influences the amount of DDT subsequently found in the blood. If 150 μg DDT is applied topically to the coxae, using 15 μl of ethanol, up to 15 ppm DDT may be found in the blood at prostration. Allowing roaches to run until prostrate in a jar containing a deposit of 50 mg DDT/1000 cm^2 yields similar results. Both these methods are such that DDT is smeared over a considerable portion of the body. If, however, dioxane is used as the solvent, and 2 μl containing 150 μg DDT is applied to the membrane between the prothoracic legs, less than 1 ppm will be present in the blood at prostration.

The toxicity of the blood does not correlate with the concentration of DDT. That is, samples of prostrate roach blood containing less than 1 ppm DDT may be equal to or more toxic than samples containing 10 or more ppm. We have also found that toxic samples of blood have about equal effects when injected into either DDT-resistant or -susceptible strains of houseflies. The particular resistant strain of flies used in these experiments could tolerate injected doses of 5 μl of normal roach blood to which DDT had been added to bring it to a concentration of 50 ppm.

Samples of toxic blood taken from DDT-poisoned roaches, extracted several times with ether or benzene, remained toxic even though controls showed that the method would quantitatively remove DDT from blood samples containing known amounts of the compound. Thus it seems that the presence of DDT in blood from DDT-poisoned roaches is not the principal factor determining the ability of houseflies to show DDT-poisoning symptoms when injected with it.

Blood drawn from roaches will ordinarily clot, because of clumping of the hemocytes. If the blood is frozen immediately upon removal from the roach, however, it will not clot when thawed. In practice, blood was collected by cutting the antennae, applying a slight amount of pressure to the roach, and allowing the blood to drip onto a watch glass resting on dry ice. From 50 to 100 roaches yield 1 ml of blood. The frozen blood was placed in a small tube, thawed, centrifuged to throw down the hemocytes, and the clear straw-colored serum was decanted off. This was refrozen and stored in this state to prevent melanin formation.

It was apparent that, in order to study the nature of the toxin in blood from poisoned roaches, a more sensitive method of detecting its presence would be required. It also seemed desirable to find a method in which the presence of small amounts of DDT, which frequently occur in the blood, would not interfere with the detection of toxins other than DDT. Roeder and Weiant (*4*) showed that DDT induces trains of impulses in the sensory nervous system but does not induce trains when applied to the central nervous system of the roach. The fact that samples of toxic blood produced typical symptoms of DDT-poisoning suggested the possibility that it might produce abnormal effects in the sensory nervous system and possibly in the central nervous system.

The effect of toxic blood on the sensory system of the metathoracic leg was investigated by the same means used by Roeder and Weiant (*4*) for DDT suspensions and emulsions. Silver electrodes were attached to the crural nerve after exposing it by cutting the membrane at the base of the metathoracic coxa. The nerve potentials were fed into a preamplifier to a cathode-ray oscilloscope, and then recorded photographically. An audio unit allowed observations to be made without continual watch of the image on the cathode-ray tube. Blood from prostrate roaches injected through the cut end of the tibia and forced

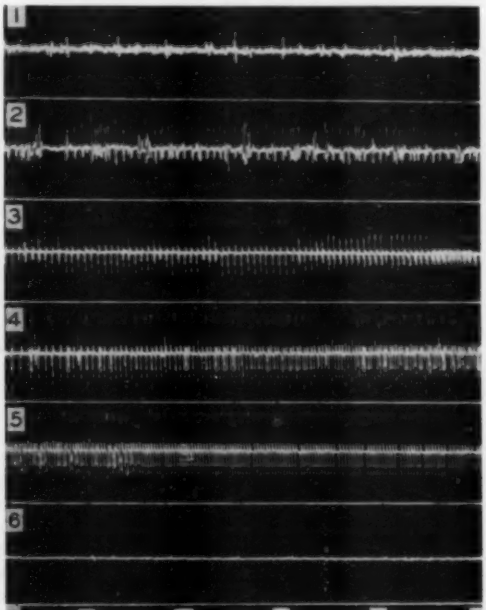

FIG. 1. Response of isolated central nervous system of American roach to blood from DDT-prostrate roaches, recorded with a cathode-ray oscilloscope: 1, normal appearance in physiological saline; 2, after 2 min in toxic blood; 3, after 5 min in toxic blood (gain reduced); 4, after 7 min in toxic blood; 5, after 7.5 min in toxic blood (gain further reduced); 6, after 8 min in toxic blood; 7, time signal, 0.1 sec between marks.

through the leg so that it appeared within the coxa caused high-frequency trains to appear within a few minutes. Blood from untreated roaches was ineffective. Since 10 ppm DDT can produce this effect within 2 or 3 min (*4*), it might be argued that the results produced by the toxic blood were due to DDT.

It was found, however, that toxic blood applied to the central nervous system would cause an abnormal response. The nerve cords used in this work were carefully dissected from adult male American roaches and placed in physiological saline. Observations of the normal activity of each cord were made by placing it in saline in a shallow groove of a plastic block, and attaching silver electrodes between the second and third abdominal ganglia. The entire unit was kept in a plastic box in which the relative humidity was near 100% to prevent drying of the preparation. After making certain that the cord was normal, the saline was drawn off, and replaced with the blood sample. Blood from untreated roaches, or from roaches treated with DDT but not yet showing poisoning symptoms, had no effect. If blood from roaches prostrate from DDT-poisoning is placed on an isolated nerve cord, an immediate increase in the normal spontaneous activity occurs, and within a few minutes high-frequency impulse trains appear. These increase in number and duration and finally become almost continuous. In most cases a sudden block of the activity follows, lasting from 1 to 15 min, after which a gradual return to normal may occur. This sequence of events is typically illustrated in Fig. 1. The more toxic samples of blood cause the build-up of trains, followed by a sudden block, to take place within 3 min. These effects are not dependent upon the amount of DDT present. Toxic samples of blood containing less than 1 ppm DDT are capable of causing this effect.

It is apparent that this method will permit the measurement of the relative amounts of toxin present even though there is considerable variation in the pattern of spontaneous activity from one nerve cord to another. The effect of toxic blood becomes unmistakably apparent by the marked increase in activity, even though it may be for a short duration in cases where the blood sample may have a low level of toxic material. The method has the added advantage of reflecting only the stimulating effects of toxins in the blood other than DDT, unless samples containing relatively large amounts of added DDT (20 ppm) are allowed to remain on the cords for periods of approximately ½ hr or longer.

It would be logical to assume that the toxic products found in the blood of DDT-poisoned roaches gradually accumulate in the blood as the symptoms of DDT-poisoning progress. It is not possible to test this assumption by injecting flies, for only the more toxic samples from prostrate roaches produce any detectable symptoms, and they may actually be the result of a combination effect with small amounts of DDT. Roaches bled in various stages of DDT-poisoning ranging from hyperexcitable to prostrate do display the progressive accumulation of a toxin in their blood, as shown by the observations recorded in Table 1.

TABLE 1

RELATIONSHIP OF STAGE OF POISONING IN DDT-POISONED ROACHES TO APPEARANCE OF TOXIN IN BLOOD

Stage of poisoning	Effect of blood on isolated nerve cord
Hyperexcitable	Cord 1: No effect. Cord 2: A few bursts of high activity at 6 min, then normal again. Cord 3: A few trains at 6 min, then back to normal.
Early prostration	Cord 4: Activity up at once. Trains at 3 min; blocked at 4 min. Cord 5: Activity up at once. Trains at 8 min; gradual return to normal. Cord 6: Activity up at once. Trains at 6 min; blocked at 10 min.
Late prostration	Cord 7: Activity up at once. Trains at 20 sec; blocked at 1 min, then came back, and repeated cycle. Cord 8: Activity up at once. Trains at 2 min; blocked at 7 min. Cord 9: Activity up at once. Trains in 1 min; blocked at 18 min.

Vinson and Kearns (*5*) have shown that roaches injected with certain dosage levels (4–12 μg/roach) of DDT may be rendered prostrate if held at a temperature of 15° C, and revived to normal behavior if transferred to 35° C. Similar results may be obtained by topical application of 75 μg DDT to the ventral membranous area of the prothorax. This suggested testing blood from roaches prostrate at the low temperature to see if it was toxic, and subsequently testing blood from roaches of the same group after revival at the high temperature to see if it lost its toxicity. The results of this experiment are shown in Table 2, where it will be seen that roaches prostrate

TABLE 2

CORRELATION OF THE EFFECTS OF TEMPERATURE ON THE REVERSIBILITY OF DDT-POISONING SYMPTOMS AND THE ABILITY OF ROACH BLOOD TO STIMULATE THE SPONTANEOUS ACTIVITY OF THE ISOLATED ROACH NERVE CORD

Time and temperature sequence before roaches were bled					Condition of roaches when bled	Effect of blood on isolated nerve cord
35°C	15°C	35°C	15°C	35°C		
20 hr					Normal	None
20 "	1 hr				Prostrate	Trains
20 "	2 "				"	"
20 "	4 "				"	"
20 "	4 "	½ hr			Intoxicated	None
20 "	4 "	1 "			Excitable	"
20 "	4 "	2 "			Normal	"
20 "	4 "	2 "	1 hr		Prostrate	Trains
20 "	4 "	2 "	2 "		"	"
20 "	4 "	2 "	4 "		"	"
20 "	4 "	2 "	4 "	½ hr	Intoxicated	Slight increase activity
20 "	4 "	2 "	4 "	2 "	Normal	None
20 "	4 "	2 "	4 "	2 "	Prostrate	Trains

at the low temperature contain a high level of toxin in their blood, which disappears after they become normal on transfer to the high temperature. The reverse is also true. DDT-treated roaches apparently normal at 35° C contain blood that will not excite the isolated central nervous system, but roaches from the same group rendered prostrate with DDT-poisoning by transfer to 15° C contain blood that will produce a high level of stimulation in the isolated nerve cord.

At present we are studying the nature of the toxin produced in the blood of DDT-poisoned roaches, the role of temperature in relation to the disappearance of the toxin, and the presence of the toxin in relation to the mechanism of action of DDT. The results of these studies will be reported in greater detail later.

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Differentiation between Circulins A and B and Polymyxins A and E by Paper Chromatography

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Circulin, a mixture of antibiotics produced by *Bacillus circulans* Q-19, consists of basic polypeptides that are biologically and chemically closely related to the polymyxins (*1–7*). In fact, Peterson and Reineke (*2*) reported that the circulin fraction that they studied most intensively (since then designated as circulin A) had qualitatively the same composition as polymyxins A and E. All three antibiotics were thought to contain L-threonine, D-leucine, L-α, γ-diaminobutyric acid (DABA), and an optically active isomer of pelargonic acid with the properties of 6-methyloctanoic acid (*8*). Unlike polymyxin A, however, circulin was inactivated in the presence of lipase. These workers had no polymyxin E available for comparative work and were therefore unable to rule out the possibility that circulin A and polymyxin E were the same.

[1] Many colleagues gave us invaluable help in this work, and we gladly express our thanks to the following: George Brownlee, formerly of the Wellcome Research Laboratories, Beckenham, Kent, Eng., for sending us a sample of polymyxins A and E, and for arranging with Tudor Jones to compare circulin and polymyxin E by paper chromatography; and Harold Nash, of the Pitman-Moore Company, Indianapolis, Ind., for his continuous cooperation and permission to use some of his unpublished data in this paper.

Peterson and Reineke obtained circulin A after repeated chromatography over a mixture of equal amounts of Dareo G-60 and Celite 545, using 25% aqueous tertiary butanol adjusted to pH 4.0, with sulfuric acid as the developing solution. This system separated crude circulin into two main components, namely, fraction A and the more rapidly moving circulin B. Using a combination of the above procedure and paper chromatography with the system to be described later, we obtained preliminary evidence that strain Q-19 probably produces, in addition to the two major components already mentioned, at least three other ninhydrin-positive, biologically active entities of as yet unknown nature. This paper records the fact that circulins A and B can be distinguished from polymyxins A and E by paper chromatography.

Preparation of the circulins. Separation of circulin A from circulin B was accomplished by the procedure mentioned above, or by the following method suggested by Nash (*9*): Impure circulin sulfate was dissolved in a minimal amount of *n*-butanol that had been saturated with a 0.1 *M* sodium citrate–hydrochloric acid buffer (pH 2). This solution was added to a column of Celite 545, which had been moistened by the buffer saturated with *n*-butanol. The developing agent was *n*-butanol saturated with buffer. The fractions collected were extracted twice with 10-ml portions of distilled water. After the biological potency of each extract was determined (*cf.*[*1*]), the appropriate extracts were pooled and concentrated *in vacuo* to a small volume. An acetone solution of picric acid was used to precipitate the biologically active material from an aqueous solution. The picrate was converted to the hydrochloride by gaseous hydrogen chloride or concentrated hydrochloric acid.

Polymyxins A, D, and E. Polymyxin A was approximately 48% pure, and its hydrochloride assayed 4800 polymyxin A u/mg. Polymyxin E regarded as essentially pure was furnished in the form of a base, and its sulfate assayed 11,600 polymyxin E u/mg before it was converted to the free base with gaseous ammonia at pH 8.2. Polymyxin D was used as hydrochloride and contained 1280 polymyxin D u/mg.

Paper chromatography. The antibiotics (usually 100 μg in 5 μl) were applied to Whatman No. 1 filter paper strips and permitted to dry. Unless otherwise indicated, the solvent system used consisted of the following: 49.5% *n*-butanol, 49.5% water, and 1.0% glacial acetic acid (*9*). The strips were hung for descending chromatography in an airtight glass cylinder and were allowed to equilibrate for about 2 hr with the vapors from the aqueous phase of the solvent system. The nonaqueous phase was then used to develop the chromatogram. Development continued for at least 60 hr. Ninhydrin was used to indicate the position of the peptides. Duplicate strips served to make certain that the ninhydrin-positive materials were actually antibiotically active. After chromatography the strips were placed for 8 min on the surface of an agar medium that had been seeded with *Escherichia coli ATCC 26* (*cf.* [*1*]), and then removed.

Following growth of the organism, the locations of the zones of inhibition were compared with those of the ninhydrin-positive areas.

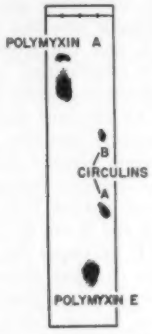

FIG. 1. Descending paper chromatogram of polymyxin A, polymyxin E, and a mixture of circulin A and B. Water, *n*-butanol, and acetic acid were used as the developing solution. In this system, in contrast to the one used by Peterson and Reineke (*2*), circulin A moves more rapidly than circulin B.

Fig. 1 shows a chromatogram of polymyxin A, polymyxin E, and an impure sample of circulin, containing both A and B, which assayed 5800 u/mg. The antibiotics were present as hydrochlorides. This figure shows that neither circulin A nor B is chromatographically identical to polymyxins A or E.

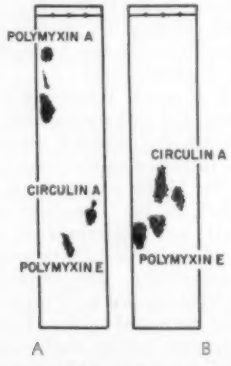

FIG. 2. Separation of polymyxin A, polymyxin E, and circulin A by descending paper chromatography. In *A* the antibiotics were applied singly, whereas in *B* single antibiotics were compared to a mixture of polymyxin E and circulin A.

Fig. 2, *A* illustrates a typical chromatogram of polymyxin A, polymyxin E, and circulin A (all as hydrochlorides). As can be seen, circulin A moved at a different rate than either polymyxin A or polymyxin E. It was possible to separate a mixture of the three antibiotics just as readily, although the individual components in a mixture sometimes moved at slightly different rates than they did when applied singly. Fig. 2, *B* shows a chromatogram of polymyxin E, a mixture of E and circulin A, and circulin A alone. The result again indicates that circulin A and polymyxin E are distinct entities.[2]

According to preliminary evidence obtained by Nash (*9*), who used the paper chromatographic procedure that he developed and that was described above, hydrolysates of circulins A and B contain isoleucine in addition to the constituents found to be present by Peterson and Reineke (*2*). Although we were able to confirm these observations, final proof for the presence of isoleucine will have to await actual isolation and identification of isoleucine or one of its derivatives.

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Manuscript received March 7, 1952.

[2] A private communication from George Brownlee to one of us (H. K.) stated that Tudor Jones, of the Wellcome Research Laboratories, Beckenham, Kent, Eng., also was able to demonstrate different rates of mobility for a relatively impure sample of circulin and polymyxin E under the conditions which he used to prepare paper chromatograms.

Colloidal Graphite in the Preparation of Samples for Gas-Flow Counting

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In tracer studies the sensitivity of methods involving isotopic dilution is a function of (1) the activity of the original preparation, (2) the sensitivity of the counting technique, and (3) the accuracy of the counting technique. Frequently the activity of the original material is limited, either by possible physiological effects of irradiation or by unavailability of highly active material. The sensitivity of β-ray counting is greatest where the material is introduced into the counting chamber, either as a gas or as a nonvolatile solid. A convenient method for accomplishing this is found in the use of the gas-flow counter (*1*), in which the sample is introduced as a solid into the counter and a stream of counter gas is flushed constantly through the chamber (Fig. 1). With relatively low sample masses, this method gives up to 50% β-ray counting efficiency.

In the application of this technique, a serious disadvantage experienced in several laboratories, including our own, has been the inherent inaccuracy of counting, as evidenced by nonreproducibility of counting rates on the same sample when counted on different days: most of the time the results would not check within statistical expectations. Even a C^{14}-polystyrene

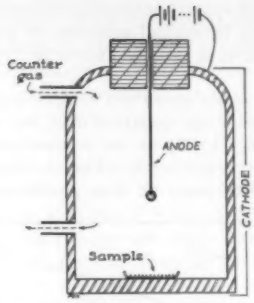

FIG. 1. Diagram of gas-flow counting chamber.

standard was erratic. Where quantitative answers were needed, much of the advantage gained by the high efficiency of counting was thereby lost. It seemed possible that this lack of reproducibility was caused by changes in the electrical properties of the counting chamber. Fig. 1 shows diagrammatically the physical arrangement of a conventional flow counter. The sample at the bottom may be introduced by the rotation of a turntable which provides a gas-tight seal. On examination it is seen that the electric field above the sample depends on the effective charge density on the surface of the sample, and that this charge density could vary from time to time if the sample had a high dielectric constant, but would remain quite constant if the sample were a good conductor. Since many of the samples are preparations which present a film with a high dielectric constant, it seemed possible that elimination of this might resolve the difficulty. Colloidal graphite, which has a high conductance per unit weight, was introduced into the samples for this purpose.

Data on typical samples illustrative of the results of incorporation of colloidal graphite are given in Table 1. In the preparation of each sample 1 ml of a slightly basic aqueous solution containing I^{131} was evaporated to dryness in a shallow aluminum sample container 2.5 cm in diameter. Where graphite was incorporated, 0.05 ml of a colloidal graphite solution containing 5.5 mg of colloidal graphite was added to the solution before evaporation. The counter was operated using a helium-isobutane mixture and a 1450-v anode potential. Each of the samples was counted at two different times at least 20 hr apart under otherwise identical conditions; the values were normalized (for radioactive decay) to the same time. The values for the graphitized samples reproduced within statistical limits; the values for the nongraphitized samples did not. All other samples graphitized and tested as described above have shown counting reproducibility. A thin sheet of aluminum was mounted over the C^{14}-polystyrene standard; following this its erratic counting behavior disappeared immediately.

It is evident that presentation of a conducting surface by a sample improves its counting reproducibility in a flow counter. This means an over-all increase in accuracy of counting determinations which may mean, as it has for some projects in our laboratories, the difference between using and not using the gas-flow counting technique. The colloidal graphite concentrations used in the examples are not necessarily optimum for all purposes and may be reduced for greater sensitivity in counting very weak β-rays.

TABLE 1

REPRODUCIBILITY IN THE GAS-FLOW COUNTER OF SAMPLES WITH AND WITHOUT COLLOIDAL GRAPHITE

Sample			Without graphite		With graphite (1.1 mg/cm²)	
Main constituent	Mg/cm² without graphite	Day	Total counts	Counts/min ± P.E. (corrected)	Total counts	Counts/min ± P.E. (corrected)
Sodium chloride	0.10	1	27,069	4980 ± 20	25,023	4616 ± 20
		2	23,888	4790 21	23,032	4620 20
Serum solids	0.30	1	6,918	467 4	8,869	313 2
		2	2,994	325 4	6,754	314 3
Serum solids	0.30	1	8,873	481 3	16,326	628 3
		2	5,600	650 6	6,754	631 5

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A Method for Quantitative Evaluation of the Effects of Ionizing Radiations on Growth of Adenocarcinoma *in vivo*[1]

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In estimating the inhibiting effects of ionizing radiations on the growth of tumors *in vivo*, one customary practice is to observe the fraction of tumors completely regressed at a given period following the irradiation. When the radioresistance of the tumor is high, this fraction is small, and any quantitative as-

[1] Supported by grants-in-aid from the National Cancer Institute of Canada.

sessment of effects based on such data is subject to a high degree of statistical uncertainty. An alternative method, often used in the assay of the effect of drugs, is to make the daily growth rate the criterion. Since this quantity depends on the existing size of the tumor, this method also suffers from large sampling error unless the number of animals used is quite substantial. This latter practice is not always feasible under ordinary laboratory conditions.

Recently, in the course of investigating the biological effectiveness of the x-radiation from the betatron on the regression of mouse tumors, it was noted that adenocarcinoma E0771 transplanted by the usual trocar method and measured externally by calipers, grew at a constant rate according to a simple expression originally derived by Blum (*1*). As seen in Fig. 1, the control tumors grew at a constant rate

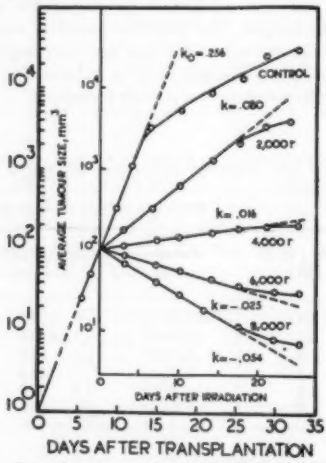

FIG. 1. Growth curves of mouse adenocarcinoma E0771. Each group, consisting of 20 tumors, was given a single dose of 200 kv x-radiation. Note the linear portion of each curve fits the growth function, $\log V/V_o = kt$, where V is the volume of tumor at time t, V_o is the initial volume, and k is the growth constant.

k_o from the time of transplantation until reaching a size of about 5 cm³, beyond which there was a gradual drift from the predicted course. Morphological examination revealed that this latter effect was caused by cyst formation, necrosis, and peripheral ulceration. Irradiated tumors grew at a constant but reduced growth rate, and the reduction in growth rate (decreased slope) increased with increasing dosage of radiation. With larger dosages, the slope was negative (the tumor decreased in size). At $k = o$, the growth rate of the treated tumor remained stationary, the result of an exact replacement of those cells destroyed by radiation with those formed by the few survivors able to maintain their normal carcinogenic activities. With the irradiated tumors also, following the initial period, there were significant departures from the theoretical curves. This may be attributed mainly to the fact that a few cells which escaped injury because of the statistical spatial distribution of ionization were able to multiply by normal processes of proliferation. This phenomenon is usually known as "recovery" in radiotherapy.

In order to relate quantitatively the degree of biological effect with the radiation dose, one may define a ratio $K = (k_o - k)/k_o$ as the regression index and plot this quantity against the dose. As shown in Fig. 2, the dose-effect curve in this particular case was

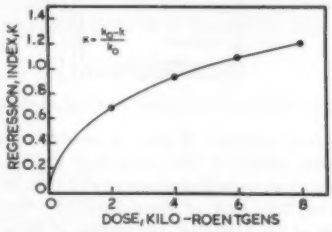

FIG. 2. Dose-effect curve fits the empirical equation $D = aK^b$, where D = dose in kilo-roentgens, K = regression index, and a and b are constants. Mouse adenocarcinoma E0771, 200 kv x-radiation.

found to follow the empirical equation $D = aK^b$, where b is a function of the biological material used and a is a constant depending on the type of radiation alone, being numerically equal to D at $K = 1$. If the same tumor is used to compare the biological effects produced by two types of x-radiation, indicated as 1 and 2, respectively, then the relative effectiveness of the former with reference to the latter is as follows:

$$\eta = \frac{D_2}{D_1} = \frac{a_2 K_2{}^b}{a_1 K_1{}^b}.$$

If, then, the two types of radiation are compared for the same growth rate ($K_1 = K_2$), $\eta = \frac{a_2}{a_1}$, and its value is independent of the degree of biological effect chosen for this comparison, and consequently may be evaluated at very low dosage range. This does not follow if b, dependent on the biological material, is found to vary with the type of radiation. In this case, it would be necessary to limit the comparison to the unique value of K at $k = o$.

With mouse adenocarcinoma E0771 as the test object, the feasibility of this method has been demonstrated in the evaluation of the biological effectiveness of the 23.5-mev x-radiation as compared with the conventional 200-kv x-radiation. A detailed report of the results obtained with this method will appear elsewhere (*2*). Suffice it to say that the value of η obtained in this way was found to agree within the accuracy of the experiments with that obtained by using lethal regression as the criterion, where a much higher dosage range was required to produce any observable effect.

The above method is preferable to existing methods for several related reasons. One major advantage is the measurability of the effect produced by a dose far below that required for a lethal effect. This is par-

ticularly valuable where the tumors are so resistant that administration of a massive dose of sufficient magnitude to produce complete regression is not practical. Elaborate measurements are reduced to a minimum because of the shorter period of observation required. Sampling errors arising from variation in tumor size are avoided, since such variations have little effect on the slope of the growth curve as long as the observation is confined within the interval where the growth rate remains constant. This difference is obviously due to the fact that, theoretically at least, lethal regression will not occur until all the cells in the tumor are affected lethally, whereas relative reduction in growth rate as in the present method is sufficient to indicate an effect. Frequently, resumption of growth at an accelerated rate takes place after a latent period following the administration of a sublethal dose. An example of this nature has also been observed when treatment of this tumor with guanazolo is discontinued (*3*). Such a phenomenon, when it occurs, renders both lethal regression and daily growth rate useless as criteria for the quantitative appraisal of the effect of the therapeutic agent.

As a prerequisite to the applicability of this method, both the control and irradiated tumors must grow at a constant rate for a sufficient period immediately after the irradiation. Under these circumstances, it is noted that change of slope k with dose is independent of the time interval, even though the growth of the irradiated tumor relative to that of the control tumor at any subsequent time may decrease appreciably with this interval.

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The Effect of Anesthesia upon Adrenergic Blockade[1]

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In a number of instances the author has observed effects of adrenergic blocking agents in trained unanesthetized dogs which did not seem to be in accord with the pharmacodynamic effects reported for such drugs (*1*). Since the usual procedure for determining the effects of such drugs is to measure changes effected in the responses of anesthetized animals, it was deemed necessary that a comparative study be made on anesthetized and unanesthetized animals using identical techniques in both.

Epinephrine and nor-epinephrine were used as constricting agents. These were injected into the carotid artery so that only the constricting effect on blood vessels was measured. A dose of 0.1 μg/kg was used, since it causes a constriction in the blood vessels of the ear equivalent to that produced by a standard intravenous dose of 2 μg/kg. Section of the sternocleidomastoid muscle and suturing it beneath the common carotid artery make intra-arterial injection a simple procedure in trained unanesthetized dogs. Vascular volume changes in a section of the ear were measured, using a photometric technique employing a photomultiplier tube (RCA 931A) and recording the output from this tube with a string galvanometer. Mean blood pressure was recorded by a membrane manometer with its lever suspended in the light beam beside the shadow of the galvanometer string. The photomultiplier tube was activated by a white light which passed through an area of the ear measuring 5×15 mm. The light intensity was adjusted so that the control output from the tube was between 15 and 20 mv. Changes in caliber of the blood vessels in this area are recorded in arbitrary units representing 0.1-mv change in the output of the tube.

An attempt was made to select the same area of the ear for each assay. However, there were day-to-day variations in the amount of light required to produce the same activity of the phototube. This probably indicates that the volume of blood in the vessels of this area of ear varied from day to day. Moderate asphyxia produces only minimal changes in the light transmission when this technique is used and does not influence the results.

The degree of constriction produced by epinephrine and nor-epinephrine in control experiments was relatively constant. In the trained dogs after control values were established, the degree of constriction was measured after adrenergic blockade, using a β-chloroethyl amine (SY 28, 2 mg/kg) and an ergot (D.H.O. 180, 0.2 mg/kg).

The results of these procedures are shown in Table 1. Each figure represents the average of 8–10 experiments. It is quite evident that, when an animal is anesthetized, either SY 28 or D.H.O. 180 is effective in reducing the degree of constriction produced by either test compound. However, if animals are not anesthetized, adrenergic blockade has little effect on the constrictor action. The slight difference between average control responses of anesthetized and unanesthetized dogs is not significant. In this study D.H.O. 180 seems somewhat more effective in blocking constrictor action than SY 28. As little as 0.006 μg/kg of epinephrine caused a measurable constriction when injected into the carotid artery.

The results on anesthetized dogs agree with those of Folkow *et al.* (*2*), but differ from those of Bülbring and Burn (*3, 4*). I also agree with Folkow that on rare occasions one finds a dilator response following the intra-arterial injection of epinephrine. One more commonly finds dilatation in the unanesthetized dog without adrenergic blockade. Such a response may be reversed in less than ½ hr, for no apparent reason

[1] Most of the research here reported was done in the Department of Pharmacology, Temple University, aided by a grant from the Smith, Kline, & French Laboratories.

TABLE 1

VASCULAR VOLUME CHANGES IN THE DOG EAR FOLLOWING INTRA-ARTERIALLY INJECTED ADRENERGIC HORMONES

Hormone	Degree of constriction*			
	Control	After SY 28 (2 mg/kg)	After D.H.O. (0.2 mg/kg)	After both agents
With anesthesia				
Epinephrine	21.2 ± 7.1	7.3 ± 2.1	3.4 ± 2.4	0 ± 0
Nor-epinephrine	13.0 ± 2.8	2.9 ± 2.1	2.0 ± 1	1.0 ± .2
Without anesthesia				
Epinephrine	23.4 ± 6.8	24.3 ± 10.6	22.1 ± 6.8	19.3 ± 7.6
Nor-epinephrine	15.8 ± 14.2	13.7 ± 8.4	18.5 ± 8.2	15.3 ± 2.9

* Each unit represents 0.1 mv change in output of photomultiplier tube.

that the author could determine. Occasionally biphasic responses are obtained in which a slight and brief dilatation precedes the constriction.

The inability of adrenergic blockade to prevent constriction in cutaneous vessels is very striking, and this is true in spite of the fact that the blood pressure response to intravenously injected epinephrine is reversed equally in both anesthetized and unanesthetized dogs.

It seems that the normal body is able to sensitize cutaneous blood vessels to either the constrictor or dilator effects of epinephrine. This control is lost in experiments on denervated vessels and in some experiments on anesthetized animals, where it is also possible to depress the constrictor effect by adrenergic blockade. However, the unanesthetized dog apparently neutralizes the effect of the blocking drug to some extent by sensitizing the vessels to the constrictor effect of epinephrine.

Further study of the vessels in other tissues is being made in order to explain these phenomena.

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Comments and Communications

Cooperation between Systematists and Experimental Biologists

IN THE recent excellent collection of papers making up the Michaelis memorial volume, *Modern Trends in Physiology and Biochemistry* (New York: Academic Press [1952]), produced by the staff of the physiology course at the Marine Biological Laboratory, Woods Hole, there appears a footnote (p. 339) by Dr. Wald which poses a problem and a challenge to those who would like to see a healthy cooperation between experimental biologists and their fellow-workers in taxonomic fields. This footnote, although extremely humorous and to the point, reflects a widespread, although by no means universal, state of mind among experimental biologists, and, indeed, complaints of this sort have of late become as familiar around Woods Hole as the cries of the sea gulls, but not so easily ignored. The gist of the difficulty seems to be that repeated changes in the names of animals long used in experimental work have caused so much confusion that busy physiologists simply can no longer follow them and might as well ignore them. The examples cited of the mandrill and Guinea baboon, and of *Limulus* versus *Xiphosura*, hardly represent contributions by taxonomists to a stable nomenclature, but to conclude from such extreme cases that name changes in general must be deplored would seem to indicate that physiologists are not fully aware of the problems of the systematist, nor of the conventions of zoological nomenclature. It is equally true that on numerous occasions systematists have revised the names of animals in very common experimental (or commercial) use without publishing clearly in journals accessible to experimentalists the reasons for the changes.

The problem expressed by Dr. Wald affects experimentalists and taxonomists alike, and at some risk of being caught in the ensuing cross fire, I shall try to point out certain reasons for the present lack of cooperation, and to suggest a positive step toward a lessening of the existing confusion. Not being a taxonomist, I should make clear that I am interested, not in the oversimplification of genuine nomenclatural problems, but rather in promoting a workable and beneficial relationship between experimentalists and taxonomists.

Experimental biologists should realize that there are two very different aspects of the problem of naming organisms. One is the matter of *nomenclature*, which is at its simplest the task of assigning a name to each distinct species of plant or animal.

Stability can be achieved here, at the level of the species, relatively readily, although there must remain numerous problems of synonymy, inadequate description, misidentification, etc. When Dr. Wald states that, "The most important thing about a name, after all, is that it remain attached to the thing it designates," he is thinking chiefly of the naming of species. But there is a second and more basic aspect to this problem, and that relates to *taxonomy,* or *systematics,* which deals with the evolutionary relationships of organisms. And it is in this respect that stability of nomenclature, as it affects genera and higher categories, cannot be asked for except at the cost of a static systematics. One can no more ask that generic names be stabilized entirely than he can ask that atomic weights or other physical constants be rounded off to integers or be not subject to revision. Major efforts to stabilize nomenclature are currently going on, but absolute stability is neither possible nor desirable.

Actually, most of the name changes which plague the experimental biologist are not changes of specific names, but revision and reordering of genera and higher groups in the attempt to evolve a more natural classification—the same goal as that of the biochemical evolutionist. The change from *Dolichoglossus kowalevskyi* to *Saccoglossus kowalevskyi* is a case in point, representing an advance in the understanding of the group as a whole. If all workers were to use the specific name, *kowalevskyi,* in their papers, and also the name of the describer (A. Agassiz), much of this confusion would be avoided. The basic rules governing such changes are no more complex than, say, those for the naming of organic compounds, and can be (and often are) covered in elementary biology courses or learned in less than an hour. There are, of course, many historically tangled nomenclatural problems requiring study by experts and suspension of the rules for their resolution. The point I wish to make is that *most* of the nomenclatural problems affecting nonsystematists are not so complex and could be explained easily in a three-line footnote. Proper use of specific names in experimental papers is likewise an essential part of the task of keeping confusion at a minimum. It should be realized that an older name can be perfectly understandable and in a sense valid, if stated in proper form. Thus the names *Platynereis megalops* (Verrill) or *Nereis limbata* Ehlers, if applied to animals at Woods Hole, introduce no confusion in spite of the fact that recently some systematists feel these to be synonyms of the earlier-described *Platynereis dumerilii* (Aud. and M. Edw.) and *Neanthes succinea* (Frey and Leuckart), respectively. If the latter, less well-known, names are used, the insertion of a brief note will make the situation clear to the general biologist.

At this point the physiologist may well ask how an experimentalist is to know whom to consult (as among physiologists, there are not only specialists among taxonomists, but good and bad taxonomists as well). How can he be sure of getting a simple, clear, and conservative answer, rather than a lengthy, overdetailed, and pedantic discussion? How can he avoid overhasty or poorly supported name changes? Obviously the taxonomist who advises an experimentalist must have a sense of responsibility in furnishing a succinct and clarifying explanation in cases where confusion exists.

The general problem can be met if those concerned wish to take simple steps to avoid lack of understanding and confusion in the future. Indeed, some positive steps need to be taken at once, if progress in the newer fields of biochemical evolution and comparative physiology is to interact to mutual advantage with advances in the older field of systematics. The step I would propose is twofold: First, for the editorial boards of journals in experimental and general biology to insist that organisms which are the subject of investigations be properly named (including species, if identifiable, and the authority), with a brief footnote clearly stating any outstanding synonymy. This is in line with the common requirements that statistical work be checked. Second, for the Society of Systematic Zoology to recruit small panels of broad-minded systematists who would undertake to verify or to furnish upon request these explanatory footnotes. This young but active society could readily supply the small but vital amount of taxonomic consultation necessary. The general problem is one that could advantageously be made a topic for discussion and action by the American Society of Zoologists at forthcoming meetings. It is not a partisan matter, but a common need of modern biologists.

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The Atlantic Estuarine Research Society

ONE day in April 1949 a group of 22 young scientists met in Morehead City, N. C. They had received their training in widely separated parts of the United States but now had a common interest—they were engaged in research related to the important fisheries of Chesapeake Bay, the North Carolina sounds, and their estuarine tributaries. Among the group were biologists, working chiefly with the oyster, the blue crab, the shad, and the croaker, and physical and chemical oceanographers, occupied with problems concerning the circulation of these semienclosed bodies of water, and with the exchange of water and dissolved substances between the rivers and the sea.

At these informal discussions it was generally agreed that the objects of the diverse investigations were ecological in nature. Furthermore, it was apparent that many unique problems were represented, for the fishery resources of this region are exploited almost entirely within estuarine waters. In almost no other region in the world do estuarine waters produce so much protein food.

Concerned with the scarcity of knowledge of the

chemistry, physics, and biology of such enclosed waters, and faced with the need for discussion of mutual problems, the group organized the Atlantic Estuarine Research Society. Enthusiasm, informality, and active participation by all members are keynotes of the organization. Its growth has been rapid, partly because research activities have been expanded in the area, and also because others outside the states of Maryland, Virginia, and North Carolina have become interested.

The stated purpose of the society is to exchange ideas and knowledge, and to stimulate free and informal discussion on estuarine ecology. Membership is restricted to scientists, whatever their field of interest, who are carrying on active research on estuarine problems. Meetings are held twice yearly, in spring and fall, and are restricted to Maryland, Virginia, and North Carolina.

The informal atmosphere is fostered by meeting at the various research laboratories. The membership believes that the strength of the organization lies in its local character, relatively small membership, and frequent meetings. Evidence that these restrictions do not impose a lack of breadth on the society is revealed by the biographies of the 73 active and 8 honorary members, who hold degrees from many different colleges and universities in North America, from the Pacific to the Atlantic coast, and from Canada to the Deep South.

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Use of Sodium Metabisulfite as a Preservative for Grass Silage[1]

SULFUR dioxide has been used extensively as a preservative for grass silages during the past few years, apparently with considerable success. Satisfactory preservation of the nutrients of the grass is obtained by addition of 5 lbs of gaseous SO_2/ton of fresh material, producing highly palatable, good quality silage at a considerably lower cost than that resulting from the use of other preservatives.

When sulfur dioxide is used in the preservation of foods, it is generally applied as an acid sulfite of calcium or sodium, in powder or crystalline form, which is more convenient to work with than gaseous or liquid SO_2.

With this in mind, preliminary experiments were conducted during the summer of 1951 to investigate the use of a concentrated water solution of sodium metabisulfite as a preservative for grass silage. This material is available in large quantities, at approximately half the cost of liquid SO_2 (per unit of SO_2). A variety of grasses and legumes were ensiled in 1-gal glass jars fitted with rubber stoppers and water traps arranged to allow seepage and escape of gases and to exclude air. In every case the silages preserved with $Na_2S_2O_5$ kept at least as well as comparable materials treated with SO_2 gas at equivalent levels, and much better than untreated control samples.

In addition, a small experimental silo ($3' \times 8'$) was filled with third-cutting alfalfa (pure stand), to which sodium metabisulfite was applied in water solution at a rate of 8 lbs/ton of fresh material. The product removed from the silo at the end of 3 months was an apparently excellent quality silage, of a color similar to that of the fresh alfalfa, possessing a clean, acid odor. This silage was eaten with considerable relish by a group of sheep over a period of more than a month, at a rate of about 8 lbs/day/100 lbs live weight.

It is recognized, of course, that these results are too meager to warrant recommendation of this product for use by farmers as a general practice. However, the experiment resulted in adequate preservation of the forage crops treated. Further work is planned to investigate the use of sodium metabisulfite in powder form under different conditions.

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[1] Authorized for publication on March 31, 1952, as paper No. 1727 in the Journal Series of the Pennsylvania Agricultural Experiment Station.

The Evidence for Mitotic Spindles in Bacteria

IN a recent report in this journal, of a meeting of the National Academy of Sciences, DeLamater (*1*) puts forward a claim to describe typical mitotic spindles in bacteria. This work was published simultaneously in a variety of journals, for the most part with identical photomicrographs (*1–5*). It is particularly worthy of notice, in view of the positive nature of DeLamater's claims, that all of these papers are illustrated by the same photomicrograph of what is alleged to be a metaphase spindle, and that in nearly all of them it is the only example shown. This figure is compared with others, published by other workers, of the same genus (*Bacillus*) in Fig. 1: 1–5, showing clearly that DeLamater's interpretation is fallacious. The supposed "centrioles" are merely the strongly stained granules at the junction of the cell wall and cross-walls of the bacillus; these cross-walls and septa, with which bacilli of this type are liberally provided, are clearly described in three standard monographs upon bacterial cytology (*6–8*). It is remarkable to be obliged to record that DeLamater, despite repeated quotation of these studies in his list of references, makes the elementary mistake of regarding *Bacillus megatherium* as a single, multinucleate cell. The present writer has repeatedly drawn attention to the misconceptions that have arisen from failure to recognize this multicellularity in bacteria (*6, 9, 10*).

DeLamater's failure to recognize the true nature of the structures he describes is due to his exclusive employment of a technique of dehydration in freezing alcohol which, he claims, preserves the material unaltered. He provides no controls of undehydrated

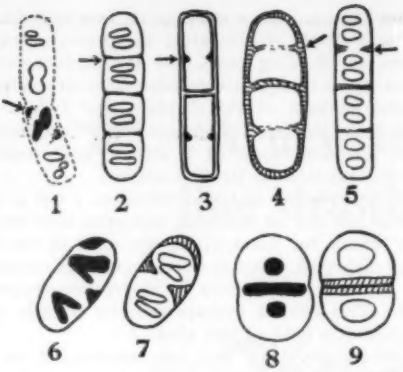

FIG. 1. 1: "Metaphase spindle" in *Bacillus*, according to DeLamater. Drawn after the photomicrograph. This figure is the sole illustration of what is claimed to be the metaphase in the majority of the papers quoted (*1–5*). The "centriole," indicated by the arrow, is seen to be identical with the granules at the junction of the cell wall and cross-walls in 2–5. 2: *Bacillus*, according to Bisset (*6*). 3: *Bacillus*, cell walls according to Knaysi (*7*). 4, 5: *Bacillus*, according to Robinow (*8*). 4, cell walls; 5, septa and nuclei. 6, 7: *Bacterium coli*, claimed by DeLamater to show mitotic spindle; 6, as seen; 7, showing nuclei, growing tip, and points of division. 8, 9: *Coccus*, showing appearances claimed as mitotic spindle by DeLamater; 9 shows that the "centrioles" are the shrunken nuclei; the "chromosomes" are a cytoplasmic septum.

preparations in support of this contention, however, and it is the experience of the present writer that this method, in common with all dehydration techniques, is very liable to produce shrinkage and distortion in bacteria (*11*).

Of the appearances in other bacteria described by DeLamater, those in *Caryophanon*, which is a very strongly septate organism, are susceptible to the same explanation as in *B. megatherium*. In *Bacterium coli*, the "centrioles" are provided by the material which, in a nonseptate bacterium, corresponds to the septa in *B. megatherium*—i.e. the basophilic areas at the points of division and growing tips of the cell (Fig. 1: 6, 7). In cocci, which frequently possess a central, transverse septum, the shrunken nuclei are apparently seen as "centrioles," the basophilic elements of the septa as chromosomes (Fig. 1: 8, 9).

The facts thus show, fairly conclusively, that DeLamater's claim of having demonstrated mitotic spindles in bacteria is entirely invalid because (*a*) the fundamental fact that most of the bacteria described are multicellular is ignored; (*b*) proper controls for experimental methods are not submitted; (*c*) the evidence utilized to support the contention is exceptionally flimsy and rests very largely upon the repeated publication of a single photomicrograph, claimed to represent a "metaphase spindle," the true explanation of which is shown in the diagrams of Fig. 1.

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Book Reviews

Cold Injury. Transactions of the First Conference, June 4–5, 1951, New York. M. Irené Ferrer, Ed. New York: Josiah Macy, Jr. Fdn., 1952. 248 pp. $3.25.

This volume presents a well-balanced résumé of experimental studies and creative thoughts on cold injury and should be of interest to investigator administrator, and physician. The aim of these conferences is not only to further knowledge about cold injury, but also to promote communication between scientific disciplines. The integration of scientific knowledge, using the multiprofessional approach, is the objective of the Macy Foundation.

Shumacker and Crismon summarize their animal studies in the first two papers. The physiological and biochemical changes occurring in frozen tissue are defined, and the rationale of rapid rewarming is critically discussed. Lewis (R. B.) summarizes his observation on muscle necrosis caused by frostbite and presents his concept of cold injury—namely, that it is due to a lethal effect of cold on tissue and that the vascular system plays little or no part in the process. Behnke, Bureh, Blair, and Shumacker defend the role of the blood vessels vigorously. Burton very properly emphasizes the importance that physical factors, such as viscosity of blood, play in the chilled extremity. There is a discussion of the physics and kinetics of water crystallization.

Homeokinesis is discussed by Horvath, and Talbott (the conference chairman) draws on his extensive clinical experience to define the renal and cardiovascular physiology of hypothermia. Dangers during the rewarming period are analyzed.

Kark summarizes the present knowledge on ac-

climatization. Blair presents his observations on acclimitization to cold in animals. This is stimulating work, because he has reproduced frostbite using only low ambient temperatures. The lesions are closely comparable to those seen in man under field conditions. Sellers' studies confirm those of Blair in every particular, and his reproduction of partial acclimatization by thyroxin and cortisone is an important advance.

This book is recommended by three further features: Edholm's discussion of the hunting reaction (the finest since that of Sir Thomas Lewis in 1931), Fremont-Smith's knack of asking pointed questions and of summarizing problems, and the editing of Ferrer. Complete indexing and 185 selected references make it a significant, up-to-date, usable reference book on cold injury.

DURWOOD J. SMITH
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Absorption and Extraction. 2nd ed. Thomas K. Sherwood and Robert L. Pigford. New York–London: McGraw-Hill, 1952. 478 pp. $7.50.

This book is a complete and welcome revision of the useful first edition published in 1937. In the intervening 15 years the text has grown from 278 small pages to 478 larger ones, and this increase in size well represents the amount of valuable information added in the new edition.

The authors have been successful in presenting a survey of the field of gas absorption, which relates the work on many diverse aspects of the problem to the main purpose of designing absorption equipment. Except in the case of the most important concepts, the exposition is not detailed. The general outline and the value of the subject matter are presented, and the student is left to work out the details of the subject, or he may consult the references given. In recent years, there has been a tendency in engineering texts to work out every possible problem and save the reader the necessity of looking up or thinking out anything for himself. The method employed in this book is, in this reviewer's opinion, much to be preferred.

The first chapter covers molecular diffusion and generally resembles that of the first edition. The second chapter is new; it deals with eddy diffusion and turbulent flow and is an important addition to the text. Chapter III is concerned mainly with the analogies among heat, momentum, and mass transfer; it contains references to much new data which help illustrate the usefulness of the methods discussed. There is a new chapter on simultaneous heat and mass transfer, and the chapter on the principles of design has been greatly improved and brought up to date. The authors allotted about the right amount of space to coefficients and to transfer units.

The section on the design for multicomponent systems has been changed to include more and better material on equilibrium relations in these systems. The various methods of estimating the pressure drop in towers, the flooding point, and the performance of various types of equipment under different conditions are the subjects of the chapters that follow. The chapter on simultaneous absorption and chemical reaction has been expanded to include much practical data not available in the first edition.

The final chapter on liquid extraction is not as complete as the rest of the book, but even here the authors' knack for summarizing the state of the field is well displayed. There is a short appendix concerned with the economic factors in absorption equipment design. This subject perhaps deserves a little more attention in a book of this kind.

Although the book has been reviewed from the point of view of a graduate text in chemical engineering, it should be added that it is a valuable reference work and should find a place in the library of most engineers.

C. O. BENNETT
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Purdue University

Scientific Book Register

The Tertiary Cheilostomatous Polyzoa of New Zealand. David Alexander Brown. London: British Museum (Natural History), 1952. 405 pp. £4 10s.

The Practical Significance of Modern Cardiological Investigations. T. E. Lowe, H. B. Kay, and H. A. Luke. Victoria: Melbourne Univ. Press; New York: Cambridge Univ. Press, 1951–52. 206 pp. $7.50.

Land for Tomorrow: The Underdeveloped World. L. Dudley Stamp. Bloomington: Indiana Univ. Press; New York: American Geographical Society, 1952. 230 pp. $4.00.

Introduction to the Study of Physical Chemistry. Louis P. Hammett. New York–London: McGraw-Hill, 1952. 427 pp. $6.00.

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Meetings & Conferences

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Aug. 11–15. National Medical Association. Chicago.
Aug. 15–22. International Conference of Agricultural Economists. East Lansing, Mich.
Aug. 17–23. American Pharmaceutical Association. Hotel Bellevue-Stratford, Philadelphia.
Aug. 17–23. International Grassland Congress. Pennsylvania State College, State College.
Aug. 18–22. Seminar in Industrial Instrumentation. Minneapolis-Honeywell Regulator Company, Philadelphia.
Aug. 19–22. American Institute of Electrical Engineers (Pacific General). Hotel Westward Ho, Phoenix, Ariz.
Aug. 20–27. Australian and New Zealand Association for the Advancement of Science (Annual). Sydney.
Aug. 20–28. International Congress on Theoretical and Applied Mechanics. Istanbul.
Aug. 21–23. Alaska Territorial Medical Association, Anchorage.
Aug. 22–30. Australasian Medical Congress. Melbourne.
Aug. 24–27. International Union against Tuberculosis. Rio de Janeiro.
Aug. 24–30. International Congress on Diseases of the Chest. Rio de Janeiro.
Aug. 25–29. American Congress of Physical Medicine. Roosevelt Hotel, New York.
Aug. 25–29. Oak Ridge Summer Symposium on "The Role of Atomic Energy in Agricultural Research." Oak Ridge, Tenn.
Aug. 25–30. Pan-American Union of Engineering Societies. New Orleans.
Aug. 25–30. World Federation for Mental Health (Annual). Brussels.
Aug. 31–Sept 7. Interamerican Cardiological Congress. Buenos Aires.
Sept. 1–2. Mathematical Association of America, Inc. (Summer). Michigan State College, East Lansing.
Sept. 1–3. International Spectroscopy Colloquium. London.
Sept. 1–6. American Psychological Association. Washington, D. C.
Sept. 1–6. International Congress on Astronautics. Stuttgart.
Sept. 1–8. World Congress of Anthropology and Ethnology. Vienna.
Sept. 1–12. Biological Photographic Association. Hotel New Yorker, New York.
Sept. 2–5. American Mathematical Society (Summer). Michigan State College, East Lansing.
Sept. 2–5. Conference on Science, Philosophy and Religion. Columbia University, New York.
Sept. 2–5. Institute of Mathematical Statistics. Michigan State College, East Lansing.
Sept. 2–5. International College of Surgeons, U. S. and Canadian chapters (Annual). Conrad Hilton Hotel, Chicago.
Sept. 2–6. Conference on Magnetism. University of Maryland, College Park.
Sept. 3–9. International Union for the Protection of Nature. Caracas.
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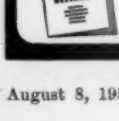

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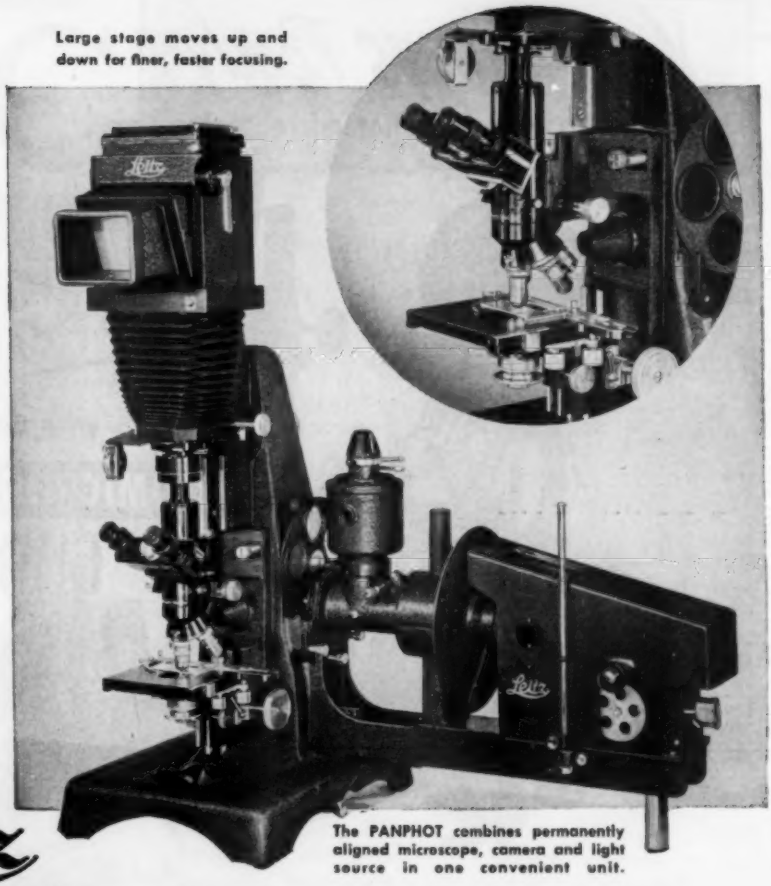

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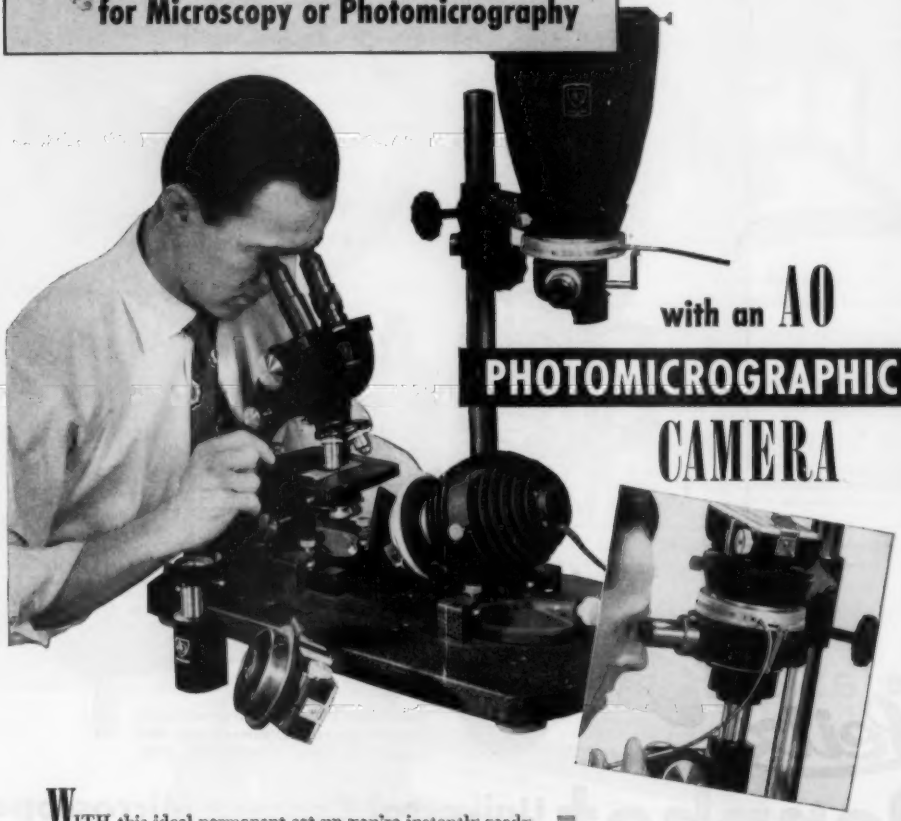

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CAMERA

WITH this ideal permanent set-up you're instantly ready for any visual or photomicrographic work. Just clamp microscope and illuminator to the AO Photomicrographic Camera base. A Special light-tight adapter and camera arm with fine adjustment positioning stop enable you to swing the camera away from the microscope and back without further adjustment. A binocular body can be used for extended observations and easily replaced by a monocular body when you take photomicrographs. The telescopic focusing eyepiece permits viewing moving specimens up to the instant the shutter is released. At a moment's notice you can switch from the camera back for 35mm black and white or color shots to the 4" x 5" unit for sharp photomicrographs suitable for technical journal reproduction. See your AO distributor or write Dept. H2.

- ★ 360° REVOLVING BODY—No revolving stage needed.
- ★ TAKES A 35MM FILM, 4" x 5" PLATES, CUT FILM, OR FILM PACK.
- ★ RUBBER VIBRATION ABSORBERS.
- ★ GROUND GLASS WITH TRANSPARENT STRIPS—For critical focusing by magnifier.
- ★ COMPENSATING LENS IN 35MM CAMERA—Matches field to 4" x 5" camera.
- ★ MICROSCOPE AND ILLUMINATOR—May be clamped in any of 3 positions.

American Optical

COMPANY

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